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RESPIRATORY MEDICINE

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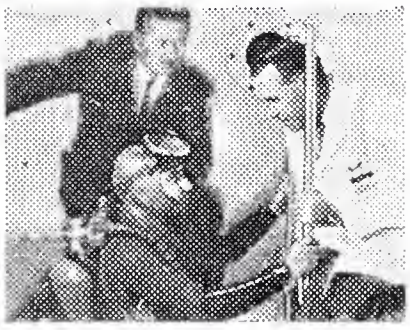

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Guest Editorial

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To Smoke Or Not To Smoke?

"A cigarette," wrote Oscar Wilde, "is the perfect type of perfect pleasure. It is exquisite and it leaves one unsatisfied. What more can one want?" A couple of today's answers might be that one would prefer not to die at such an early age or that one would prefer not to become so short of breath that the trip from the bed to the bathroom is a nightmare of dyspnoea and fatigue.

More than a hundred years ago Oliver Wendell Holmes commented on the harmful effects of tobacco and the U.S. Surgeon General has more recently said "Cigarette smoking is the greatest preventable cause of illness, disability and premature death in this country." In Britain more than 50,000 deaths per year are directly due to cigarette smoking and these deaths cause the loss of at least 150,000 years of working life annually.

Yet our communications media continue to use skillful advertising which commonly shows attractive young people smoking and there is so often the hint that it is both socially and sexually attractive to smoke brand X. It is hard to convince teenagers of the dangers to follow in their 30's, 40's and 50's since twenty years is too far in the future. As a result a depressing number of young people have become habitual smokers by twenty.

The tobacco industry's gentle voices on radio and television are very persuasive and the industry tells us that the associations between smoking and disease have not been proven. They also point out the large revenue from tobacco taxes which go to the public purse and the hardships to the farmers which would result from any measures which attempt to reduce cigarette smoking.

They do not mention the work hours lost by people who are ill with bronchitis, emphysema or coronary artery disease, or the hardships to families whose fathers die in their forties and fifties from lung cancer. In Sunnybrook Hospital, there is a 41-bed chest disease unit where over half the patients have diseases directly related to cigarette smoking. The cost per patient day is over $75.00 and the daily cost to the community for the care of these patients is over $1500. In a year, the taxpayers of Ontario pay over half a million dollars for the effects of cigarette smoking in *this one small chest unit alone*. The cost in the province as a whole must be enormous.

Cigarette smoking is basically intense personal air pollution. The number of substances which have been identified in cigarette smoke exceeds 800 but they include harmful gases, vapours and particles. Cigarette tobacco burns at over 800°C and this accounts in part for the high number of substances. In this short review, one can mention only a few.

The harmful gases include a high concentration of carbon monoxide which commonly inactivates about 5% of the smoker's hemaglobin. A smoker excretes a significantly higher amount of carbon monoxide than the non-smoker and this has always to be measured when doing a gas transfer capacity. Another harmful gas

in cigarette smoke is hydrogen cyanide which is present in cigarette smoke at a level 160 times greater than that considered safe in U.S. industry.

The Roswell Park Memorial Institute in Buffalo uses a machine which smokes 20,000 cigarettes per day and produces a tar residue which causes cancer in animals. These tars contain more than 200 known substances of which many are known carcinogens in the aromatic hydrocarbon group including benzpyrene. There are also co-carcinogens which include long chain fatty acids and other substances.

Phenols and gases inactivate and later destroy the ciliary activity which normally moves the thin mucus blanket lining the airways. This results in destruction of the normal garbage disposal mechanism of the lung and is an important part of chronic bronchitis. When the irritating effect on the submucous glands and goblet cells is added, chronic bronchitis becomes established and may become a dreadfully disabling disease.

The relationship of cigarette smoke to emphysema is less clear. In 1963, Auerbach showed convincing correlation between smoking and the development of pathologic changes in bronchi, including loss of ciliae, gland hyperplasia, goblet cell changes and parenchymal changes with alveolar septal rupture. Almost all heavy smokers showed a high degree of septal rupture.

In the United States, there is an insecticide known as Black Leaf 50. Seventy mgm. is lethal in man if given by injection and the same amount will kill a dog if placed on its gums. The insecticide is pure nicotine and some cigarettes contain as much as 2 mgm., although in others it is as low as 0.5 mgm.

Cardiovascular changes are almost as striking. In young non-smokers, the heart rate increases after one cigarette by 20 beats per minute on the average. The vasoconstrictive effects of cigarette smoke are well known and there is a striking difference in the incidence of myocardial infarction in the smoker compared with the non-smoker.

These toxic substances have to be excreted or detoxified in some way. Hence the bladder is exposed to carcinogenic substances and the smoker runs the risk of bladder as well as bronchial carcinoma.

The protests of the tobacco industry are not tenable and often contain misleading half truths. A few examples quoted by Dr. Diehl in his book "Tobacco and Your Health" are worth mentioning. The industry states that the evidence that cigarette smoking is harmful is only statistical and therefore inconclusive. Yet the tobacco industry uses its own statistics in deciding how to spend $300 million per year on advertising. Dr. Weaver of the Rockefeller Foundation replies that the discarding of evidence because it is statistical is unscientific and unwarranted because it is the only true evidence we can have.

The industry says that no substance in tobacco smoke has been proven to cause cancer, heart disease or emphysema. This is true but it does not follow that cigarette smoke, which contains so many toxic substances, does not cause these diseases. Finally, the industry notes that life expectancy has been increasing despite increased smoking. This is true but there is a great difference between the smoker and the non-smoker which they do not mention. If one smokes two packages of cigarettes per day, the difference seems to be about eight years.

Cigarette consumption in the United States in persons over age 15 has increased from 49 per person per year in 1900 to 1828 in 1940 to 4003 in 1967. Morbidity and mortality rates have risen to an appalling degree. In Canada, the lung cancer deaths and traffic deaths are now almost the same, but the enormous suffering due to chronic bronchitis and emphysema cannot be readily measured.

It is hard to reconcile a ward round on a respiratory disease unit and a few cigarette commercials. The truth seems much clearer to the young family whose father is dying of lung cancer than it does on the TV screen showing the beauties of Marlboro Country.

With this issue the University of Toronto Medical Journal begins its 49th year of publication. There will be five issues in this volume and changes in editorial format are minimal. The first article on medical education will be in the December issue.

FRED GENTILI

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A Clinical Approach To Respiratory Failure

M. B. Kamiel, 7T2

INTRODUCTION

Respiratory failure is no less a problem than cardiac or renal failure. Acute respiratory failure is commonly associated with primary lung disease, trauma, or drug overdose. Many patients have more chronic forms of respiratory failure for which the body has to compensate with varying degrees of success.

Respiratory failure is the inability of the body to adequately oxygenate the cell, to remove carbon dioxide from body fluids, and to maintain H^+ homeostasis. Clinically it has been described as the inability to maintain normal arterial oxygen and carbon dioxide levels. Traditional limits are a Pa, O_2 below 60 mm. Hg. and/or a Pa, co_2 above 50 mm. Hg.[1] However one must correlate both clinical and laboratory findings to diagnose respiratory failure.

ETIOLOGY

Respiratory failure may be classified anatomically based upon the site of origin of a causative defect, or clinically based upon blood gas levels[3] (Fig. 1).

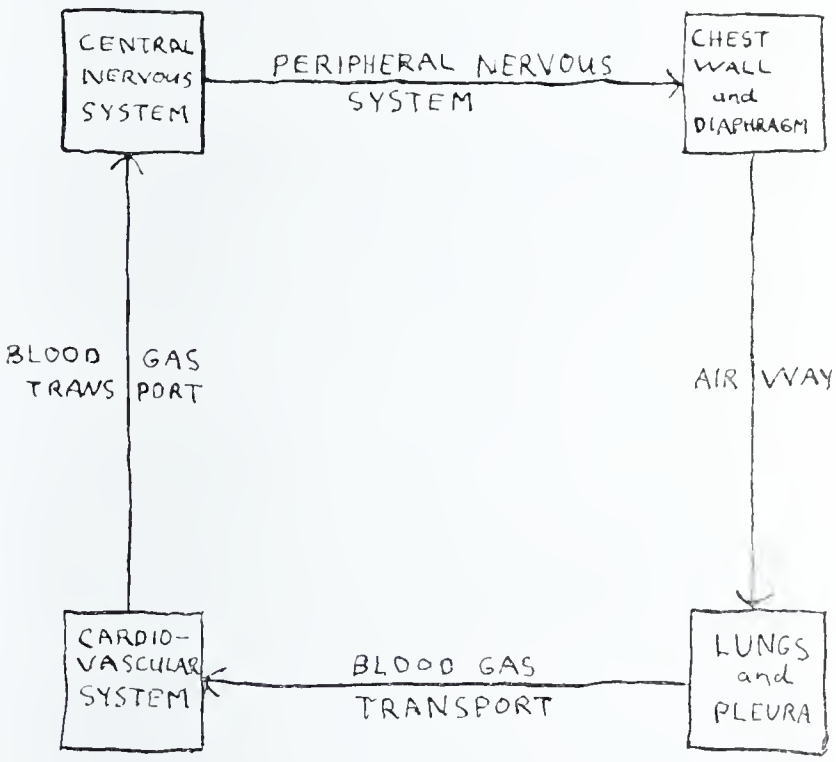

FIG. 1: Areas in Respiratory Control System where failure may be produced.

A) ANATOMICAL CLASSIFICATION

a) *Central Nervous System*
- —Brain stem hemorrhage
- —Anesthetic and depressant drugs (morphine, barbiturates)
- —Spinal cord injuries
- —Increased intracranial pressure

b) *Peripheral Nervous System*
- —Polyneuropathy
- —Guillain-Barré Syndrome
- —Bulbar Polio
- —Muscle relaxants (d-tubocurarine)

c) *Chest Wall and Diaphragm*
- —Myesthenia gravis
- —Kyphoscoliosis
- —Chest trauma

d) *Airway*
- —Upper-laryngeal edema
- —Lower-asthma, bronchitis

e) *Lungs and Pleura*
- —Lungs-atelectasis, pneumonia, emphysema
- —Pleura-pneumothorax, pleural effusion

f) *Cardiovascular System*
- —Congestive heart failure
- —Pulmonary vascular obliteraiton

B) CLINICAL CLASSIFICATION

a) *Hypoxemia without Hypercarbia*
b) *Hypoexemia with Hypercarbia*

a) *Hypoxemia without Hypercarbia*

Blood gas readings indicating hypoxemia (a low Pa, O_2) without hypercarbia (with a normal Pa, Co_2) occur mainly where there is a ventilation-perfusion (V-P) inequality. This means that ventilation and blood flow are mismatched. The solubility (and diffusibility) of a gas becomes important in this situation.[4] Transfer of medium solubility gases such as oxygen is affected more than high solubility gases such as carbon dioxide. Therefore with a mild V-P inequality the Pa, O_2 will tend to fall before the Pa, co_2 starts to rise. Furthermore, an increase in Pa, co_2 will increase respiratory drive and over ventilation. This will bring the Pa, co_2 to normal at a cost of increased work of breathing. But increased ventilation may not raise the Pa, O_2 to normal due to the lower solubility of oxygen compared to carbon dioxide[5]. Furthermore, an increase in Pa, O_2 may not result in an increased oxygen uptake by hemoglobin due to the characteristic flattening of the oxygen dissociation curve. However, a reduced Pa, Co_2 will result in a significant reduction in carbon dioxide carriage by hemoglobin (Fig. 2). In this case a state of partial respiratory failure exists. The body cannot adequately oxygenate the cell, although carbon dioxide is being removed from body fluids, and H^+ homeostasis is being maintained.

An example occurs in obstructive pulmonary emphysema[6]. Airflow obstruction from bronchitis and expiratory closure of poorly supported bronchioles, along with elastic tissue degeneration, produce lung hyperinflation. V-P abnormalities exist throughout the lung. Areas well perfused with blood but poorly ventilated lead to shunting (venous admixture) in arterial blood, thereby tending to lower Pa, o_2 and increase Pa, co_2. Areas well ventilated but poorly perfused increase the dead space, thereby wasting ventilatory work. The increased Pa, Co_2 stimulates respiratory drive leading to increased ventilation of well perfused areas. This removes shunted carbon dioxide leading to a normal Pa, co_2. Oxygen may not be added

in sufficient quantity to overcome hypoxemia as previously stated. Therefore the first blood gas changes indicate hypoxemia without hypercarbia.

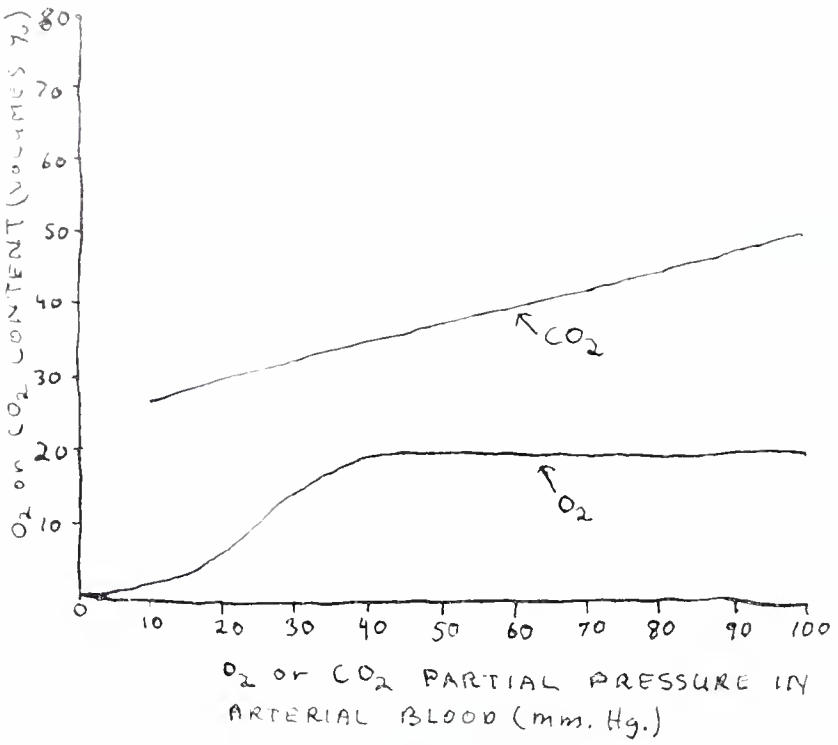

FIG. 2: O_2 and Co_2 Dissociation Curves.

b) *Hypoxemia with Hypercarbia*

Blood gas readings indicating a low Pa, o_2 and a high Pa, co_2 occur in both inequalities and alveolar hypoventilation, either on an acute or chronic basis.[4]

The main cause of carbon dioxide retention in chronic lung disease is V-P inequality where patients are unable to increase ventilation to adequate levels.[4] Furthermore, the V-P inequality seen in severe chronic obstructive pulmonary disease may result in greater impairment of carbon dioxide output than of oxygen uptake.[4]

Hypoxemia with hypercarbia may occur in a patient with normal lungs, as in depression of the respiratory centre by drugs, or in thoracic cage injury. Here, the Pa, co_2 is directly proportional to the rate of carbon dioxide produced by the body cells (Vco_2) and inversely proportional to the alveolar ventilation (Va), i.e. the amount of fresh air reaching the functioning alveoli per minute. Therefore, halving the alveolar ventilation will double both the PA, co_2 and the Pa, co_2. Under these conditions the Pa, o_2 falls, the Pa, co_2 rises, the pH falls, and the patient is in respiratory failure. However, pure hypoventilation is a relatively uncommon cause of carbon dioxide retention. Furthermore, the relationship between PA, co_2 and Pa, co_2 applies only to a normal lung.[4] In chronic lung disease the measurements will differ if a V-P inequality is present. Therefore a high Pa, co_2 does not necessarily mean that alveolar hyperventilation is present. In fact, these patients often move more air into their lungs than normal subjects.[4]

Carbon dioxide retention on a chronic basis leads to various forms of compensation. Renal bicarbonate retention may produce a normal pH though the Pa, co_2 remains high. Hypoxemia stimulates erythropoiesis leading to a secondary polycythemia.

CLINICAL FINDINGS

a) *History*

Diseases which predispose to respiratory failure must be born in mind. For example, this complication accounts for most fatalities from myesthenia gravis.[5]

Breathlessness, or the patient's awareness of diffiiculty breathing, is a common complaint in respiratory failure. It may be of acute onset related to an attack of pneumonia, or to the administration of drugs paralyzing the respiratory muscles. Obstructive pulmonary emphysema is an example of a more chronic form. After several years of chronic bronchitis with frequent respiratory infections, breathlessness on exertion may develop. It is at first present during infections, but later persists.

The presence, amount, and nature of sputum should be confirmed by observation.[6] An inadequate cough mechanism or poor ciliary action may hinder removal of secretions.

Any obvious changes in cardiac function should be noted as an idication of right ventricular failure associated with cor pulmonale. This may have an insidious onset with gradually increasing ankle and leg swelling over several weeks or present suddenly in association with an acute respiratory infection.

Knowledge of the patient's smoking habits and occupation will facilitate treatment. For example, a heavy smoker with chronic bronchitis suffers continuous irritation from tobacco smoke, increasing the chance of an attack of respiratory failure. An occupation involving noxious gas or dusts may necessitate a change.

b) *Physical Examination*

Respiratory system findings may include the inability to cough and a rapid respiratory rate above thirty-five breaths per minute. Accessory muscles such as scalenes and sternomastoids may be used. The alae nasae may flare in pneumonia. Expiration is usually prolonged in chronic obstructive pulmonary disease.

Cardiovascular system findings may reflect autonomic nervous system compensation such as sweating, tachycardia and systemic hypertension. Bradycardia and hypotension may be late findings. One should look for evidence of cyanosis in mucous membranes, signs of right ventricular failure such as a right ventricular heave, an increased pulmonary component of S_2, distended jugular veins, and dependent edema.

Nervous system findings may include irritability, loss of judgment, a gradual deterioration in consciousness, tremor and restlessness.

c) *Laboratory Studies*

1) Blood Gases and Electrolytes

When respiratory failure is suspected clinically, arterial blood gas levels (Pa, o_2, Pa, co_2 and pH) should be

obtained to confirm the diagnosis. Electrolyte levels may provide evidence of compensation.

The amount of hypoxemia can be estimated 3 ways: by knowledge of the Pa, o_2, the per cent saturation of Hb, or the amount of oxygen reaching the body cells.

Per cent saturation of Hb is determined by measuring whole blood oxygen content and subtracting from it the dissolved oxygen content of plasma, to give the amount of oxygen combined with Hb.[5] This is divided by oxygen capacity (maximal amount of oxygen combining with Hb in arterial blood) and multiplied by 100. The result is an estimate of the uptake of oxygen, and in association with the Pa, O_2 would give one point on an oxyhemoglobin dissociation curve. For example, at a Pa, O_2 of 30 mm. Hg, whole blood oxygen may be 11.5 ml./100 ml. blood. Therefore, oxygen combined with Hb is 11.5-0.1 ml. or 11.4 ml. O_2/100 ml. blood. Oxygen capacity varies with the number of grams Hb/100 ml. blood. One gram Hb can hold 1.34 ml. oxygen. At a level of 15 gm. Hb./100 ml. blood, oxygen capacity is 15 gm/100 ml. x 1.34 ml. or 20.1 ml. O_2/100 ml. blood. Per cent saturation of Hb. is then $\frac{HbO_2 \text{ x } 100}{O_2 \text{ capacity}}$ or $\frac{11.4 \text{ ml}/100 \text{ x } 100}{20.1 \text{ ml}./100 \text{ ml}.} = 57\%$.

This would indicate significant hypoxemia.

The amount of oxygen reaching body cells may be calculated by knowing the amount of oxygen combined with Hb, the cardiac output, and the oxygen requirements per minute. If oxygen delivery is less than the need, respiratory failure will be present. For example, consider a person with an oxygen carriage by Hb of 19.5 ml. O_2/100 ml. blood. If his tissue demands were 250 ml. O_2/minute, a cardiac output of

$$\frac{250 \text{ ml. } O_2/\text{minute x } 100 \text{ ml. blood}}{19.5 \text{ ml. } O_2}$$

or 1.3 L/minute blood would be necessary. If his cardiac output were less, the patient would be in respiratory failure because of the inability to adequately oxygenate the cells. The degree of hypercarbia is mainly indicated by an increased Pa, co_2.

2) Pulmonary Function Tests

These are most useful in evaluating pulmonary disease as restrictive or obstructive, and may be impossible to obtain in an acute situation. A reduced vital capacity indicates a restrictive disorder such as pulmonary fibrosis. Forces Expiratory Volume (FEV) is a test for an obstructive disorder such as asthma, indicated if less than 75% of a maximal inspiration is expelled in one second. With either restrictive or obstructive disorders, significant V-P inequalities may be present.

3) X-rays

PA and lateral studies may confirm the diagnosis of kyphoscoliosis, emphysema, atelectasis, pneumonia pneumothorax, pleural effusion, or right ventricular enlargement.

INTERPRETATION OF CLINICAL DATA

a) *Hypoxemia without Hypercarbia*

There may be minimal clinical findings to suggest partial respiratory failure. Pa, co_2 and pH would be normal, and Pa, O_2 low. There may be adequate oxygen delivery to cells as determined by cardiac output due to cardiovascular compensation of oxygen unsaturation of Hb. Cyanosis may be present at an arterial oxygen saturation of Hb below 60%. A rapid respiratory rate and/or use of accessory muscles of respiration may also be present. These findings indicate a ventilation-perfusion inequality with compensation. Treatment of the primary cause should produce a good prognosis.

b) *Hypoxemia with Hypercarbia*

The manifestations of total respiratory failure will vary depending upon rapidity of onset and upon the extent of cardiovascular and renal compensation. In this case either V-P inequality with inadequate compensation or inadequate alveolar ventilation is present.

1) Sudden Onset with Responsive Circulatory System

Pulse and blood pressure increase early. Pa, co_2 is high, arterial pH is low, Pa, O_2 is low, oxygen saturation of Hb is reduced, and oxygen delivery to tissues is almost normal. The patient may be confused and irritable from a slight reduction in the oxygen supply to body cells, or drowsy from carbon dioxide retention. Cyanosis may be present. The prognosis is good if treatment is started as soon as the diagnosis is made, and if the underlying condition is reversible.

2) Sudden Onset without Responsive Circulatory System

The pulse slows and blood pressure falls. Pa, co_2 is high, Pa, o_2 is low, oxygen saturation of Hb is reduced, and oxygen delivery to body cells is inadequate. The initially rapid respiratory rate slows markedly. Excitement and irritability are less evident due to severe reduction in the oxygen supply to cells. Drowsiness is more marked and asterixis may be present from acute carbon dioxide retention. Cyanosis may be present. Prognosis is poor unless immediate measures are taken to reverse the respiratory failure along with the underlying condition.

3) Gradual

The circulatory response is minimal or absent. Renal mechanisms compensate for a high Pa, co_2 and low pH by bicarbonate retention producing a more normal pH. Low oxygen saturation of Hb is compensated by marrow erythropoiesis producing secondary polycythemia. Oxygen delivery to cells may be adequate. Cyanosis may be

present. Although this chronic picture is commonly seen in obstructive pulmonary emphysema, there may be acute exacerbations requiring emergency care. These occur due to the particular V-P shunting seen in this disease.[4]

TREATMENT OF RESPIRATORY FAILURE

a) *Hypoxemia without Hypercarbia*

The most important aspect in treating respiratory failure is to understand the physiologic mechanism which is aberrant so that one's efforts can be properly directed.

Since the main approach is to reverse the underlying cause, general measures against reversible factors may be employed. Admission to hospital may facilitate their administration.

Recurrent pulmonary infections are common in patients with chronic pulmonary diseases producing excess secretions. Broad spectrum antibiotics may be used prophylactically. For a severe infection, culture and sensitivity should be done on an aspirated sample of tracheal secretions, and specific chemotherapy employed.

Excess secretions enhance airway obstruction. Irritants such as tobacco smoke or noxious gases should be avoided. Inhalation of steam via nembulizer and oral or parenteral iodides may reduce sputum viscosity. A program of postural drainage may help clear large volumes of secretions present chronically. In an acute situation tracheal suction is useful.

Airway resistance is increased by edema or spasm in the bronchial tree. Prophylactic bronchodilators may be used to relieve bronchospasm. These include 1:200 Isuprel administered by aerosol, or oral ephedrine, 15 to 25 mg. t.i.d. or q.i.d. Corticosteroids may be used in a patient with bronchial asthma, or with a reversible defect refractory to bronchodilators. Breathing exercises may be attempted to overcome anatomical airway obstruction. Intermittent positive pressure breathing may be useful for stimulating deep breathing, and for administering bronchodilators.

To reverse hypoxemia administration of high concentrations of oxygen is indicated as long as alveolar ventilation is adequate. Increased oxygen tension in alveoli will increase the Pa, o_2 despite V-P inequality but may only minimally increase the oxygen supply to tissues due to the flat dissociation curve (Fig. 2). The main benefit of administered oxygen is to provide a supply at minimal work cost, thereby decreasing overall oxygen consumption and reducing hypoxemia. A Pa, o_2 between 70 and 100 mmHg is most suitable.[4]

b) *Hypoxemia with Hypercarbia*

In both V-P inequality and alveolar hypoventilation, the Pa, co_2 can be reduced by an artificial increase in ventilation.[4] The underlying cause such as (kyphoscoliosis) should also be treated if possible. Hospital admission is essential in an acute situation and may be useful in a chronic one. Two stages of treatment are considered based upon whether the patient can breathe on his own or not.[8]

STAGE ONE

If the patient can breathe on his own, one attempts to provide oxygen in low concentration by Venturi mask or other such device. At first, draw blood for electrolytes and blood gases. Then monitor respiratory rate, pulse, blood pressure, cough, sputum, and state of consciousness. Treat any underlying infection or failure, and employ general measures as previously outlined.

STAGE TWO

Mechanical ventilation is employed in an acute, potentially reversible situation, when the Pa, co_2 is rising, and the pH and Pa, o_2 are falling. This provides adequate ventilation until the underlying cause is corrected. By improving blood gas composition, ventilation may restore respiratory centre sensitivity, resulting in resumption of rhythmic respiratory activity.

An endotracheal tube or tracheostomy is essential during mechanical ventilation to make suction easier, and to allow mechanical aids to be employed. The decision of which aid to use is a matter of time. An endotracheal tube is used over a short period up to 48 hours, due to danger of tracheal ulceration, and a trachostomy over a longer period. Initially, a cricothyrotomy may be necessary to establish an airway. Continue to employ general measures aimed at the underlying condition and to monitor vital clinical signs.

COMPLICATIONS OF RESPIRATORY FAILURE AND ITS TREATMENT

a) *Cor Pulmonale*

This is right ventricular enlargement secondary to a pulmonary disorder. The underlying disease is usually bilateral, diffuse, and involving both parenchyma and airways. Pulmonary hypertension is a main factor in the pathogenesis. This may be due to anatomical restriction of pulmonary vascular expansion, as in fibrosis or pulmonary vascular occlusion. Another cause is inadequate alveolar ventilation, either due to generalized hypoventilation as in respiratory muscle paralysis, or to net hypoventilatoin from V-P imbalance producing abnormal blood gas levels. Hypoxemia leads to pulmonary vasoconstriction and polycythemia, resulting in an increased load on the right heart. Hypercapnia tends to depress the respiratory centre, preventing correction of the abnormal blood gas levels by ventilation. Right ventricular end diastolic pressures are normal at first, but increase with right ventricular hypertrophy and inadequate emptying until right sided heart failure develops. Left sided pressures are usually normal. Clinical findings may be minimal before failure supervenes. Diagnosis is most reliable using x-ray and electrocardiogram. Treatment is

directed towards reversing the underlying pulmonary disorder and improving alveolar ventilation to correct abnormal blood gas levels.

b) *Acid-Base Disturbances*

Respiratory acidosis commonly occurs secondary to V-P inequality without compensation, or from inadequate alveolar ventilation whereby carbon dioxide is retained. This may be enhanced if central depression by carbon dioxide occurs.[9] Initially the pH is low, but may return to normal with bicarbonate retention by the kidney. Rest in hospital and avoidance of overexertion may reduce the metabolic production of carbon dioxide. General methods and mechanical ventilation will enhance carbon dioxide output from the lung.

Metabolic acidosis may occur during acute, severe hypoxemia whereby anaerobic glycolysis produces lactic acid. The acid tends to neutralize and reduce bicarbonate concentrations. If respiratory acidosis is also present bicarbonate will tend to be retained. Therefore bicarbonate levels will give a false indication of metabolic acidosis. Measurement of blood lactate will then be necessary. Treatment is directed towards reversing the hypoxemia.

Alkalosis may occur in the treatment of hypoxemia with hypercarbia. Mechanical ventilation will reduce the Pa, co_2 rapidly, but the plasma bicarbonate slowly. This occurs because the kidney adapts to carbon dioxide retention by bicarbonate retention and chloride excretion. Because chloride deficiency develops unless dietary chloride is high, bicarbonate excretion is slow in order that anion homeostasis may be maintained. The elevated pH may decrease respiratory drive and further impair alveolar ventilation. Prevention involves careful monitoring of blood gases and electrolytes during therapy. Administration of dietary chloride will eliminate alkalosis, restore potassium balance, and improve ventilation.[10] This occurs because in the kidney chloride is a resorbable anion while bicarbonate is not. Chloride is normally reabsorbed with sodium. In chloride deficiency, tubular sodium is only reabsorbed via H^+ potassium exchange with sodium. H^+ is depleted in alkalosis, potassium is excreted leading to potassium deficiency. Administration of dietary chloride allows sodium to be reabsorbed with chloride and thus reduces potassium excretion. Since bicarbonate is a non reabsorbable anion, it is then excreted to maintain anion homeostasis with the increased body chloride. Ventilation is improved by the reduction in alkalosis.

c) *Oxygen Therapy*

Extremely high Pa, co_2 levels may inhibit the normal respiratory centre response to carbon dioxide–pH stimulation. In these patients, impulses from hypoxemic stimulation of chemoreceptors determine ventilatory drive. Oxygen administration may inhibit the hypoxemic drive, leading to a rapid rise in Pa, co_2 and a fall in pH. Local pulmonary damage may occur from high alveolar oxygen tensions administered over a long period.

d) *Peptic Ulcer*

A peptic ulcer, usually duodenal, occurs in about 20% of patients with chronic obstructive pulmonary disease, especially in those with emphysema[6]. It may be due to gastric hyperactivity associated with hypoxemia and hypercarbia, to stress from respiratory failure and its treatment, or to steroids used as therapy to reverse airway obstruction.

SUMMARY

Respiratory failure is the inability to maintain adequate oxygen, carbon dioxide and H^+ levels in tissue. Diagnosis is confirmed by demonstrating hypoxemia without or with hypercarbia. Hypoxemia without hypercarbia is usually due to V-P inequality with ventilatory compensation. Hypoxemia with hypercarbia is most commonly due to V-P inequality, but may also be due to inadequate alveolar ventilation. Successful treatment depends upon a clear understanding of the underlying physiological or pathological process, and upon the institution of appropriate therapy. Treatment should be directed at removing the cause of the V-P inequality as well as at increasing air movement into the alveoli.

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TABLE 1 EXPLANATION OF SYMBOLS

Pa, co_2 — Partial pressure of carbon dioxide in arterial blood.
Pa, o_2 — Partial pressure of oxygen in arterial blood.
V_A — Alveolar ventilation per minute.
Vco_2 — Carbon dioxide produced by body cells per minute.
FEV_1 — Forced expiratory volume in one second.
PA, co_2 — Alveolar carbon dioxide tension.
V-P — Ventilation-Perfusion.

Bronchial Asthma: A Review

R. Greenwood, 7T2

BASIC CONCEPT

Asthma is a disease of the bronchioles in a susceptible person. Inhaled antigens, psychological stress, and infection result in the release of histamine and other agents from mast cells lying between the mucosal and bronchiolar muscle layers, causing widespread bronchiolar muscle contraction and eosinophilic mucous secretion. Consequently there is an increase in airway resistance with a secondary increase in lung volume compartments (especially residual capacity).

In an attempt to quantify the specific abnormality that distinguishes asthma from other pulmonary diseases, Jones[1] divided airway resistance into a fixed component produced by mucosal swelling and obstruction from secretions, and a labile component produced by bronchiolar constriction. Then he used the Forced Expiratory Volume in 1 second (FEV1) to obtain an index of these components in normals and asthmatics. The FEV1 was measured with the subject at rest; maximum bronchoconstriction following 8 min. of exercise was measured as a fall in FEV1 from resting. The subject was allowed to return to resting values, given some isoproterenol, briskly exercised for a few minutes and the rise in FEV1 measured. From these three values a "lability index" was obtained:

$$\text{Lability Index} = \frac{\text{Fall in FEV1} + \text{Rise in FEV1} \times 100}{\text{Predicted Normal FEV1}}$$

It was found that asthmatics have an unusually labile bronchiolar system. Their lability index value is invariably 15%, which is much higher than normal subjects. It is this lability of the bronchiolar tree that predisposes asthmatics to their attacks. Simply possessing such lability does not mean that the subject will inevitably get clinical asthma. But the highly labile subject has the potential for severe attacks, whereas the subject with slightly more than normal lability will usually only have mild asthma.

Jones found that young adults who had had childhood asthma but had beeen free of attacks for several years still retained an abnormally high lability index, regardless of the factors which were thought to have precipitated the attacks. It has not been shown yet that this mechanism precedes the appearance of symptoms, though it has been seen in young hay fever patients, many of whom later develop asthma. It would be tempting to believe that this lability of the bronchial tree is the factor that is inherited by asthmatics but this has not yet been proven. At any rate, this lability is asthma's hallmark.

CLASSIFICATION

Asthma is not a discreet entity affecting a single group, rather a common final pathway of many causes affecting different age groups. It is most commonly found in people with an inherited allergic constitution (the atopic type). This is the "extrinsic" type of asthma and it is the main form of childhood asthma. This variety occasionally regresses spontaneously as the patient reaches adulthood, though it usually persists.

In contrast "intrinsic" asthma is precipitated by infections of the upper or lower respiratory tracts usually in adults. These patients most frequently possess chronic bronchitis as well, resulting in a large fixed component to their airway resistance, leaving little reserve. Slight changes in calibre beyond this as a result of infection or stress precipitate frank asthmatic attacks.

This classification is not clear-cut, simply because many patients with long-standing extrinsic asthma develop chronic pulmonary disease which increases the fixed component of their airway resistance. And all types of asthmatics have attacks precipitated by such secondary factors as changes in temperature and humidity, exposure to air pollutants, emotional stress, and hormonal changes. This classification, though has some utility in determining management.

PATHOLOGY

Tissue damage seen in the lungs during an attack shows an allergic picture. The lumen of the bronchus is filled with mucus and cell debris. The cellular debris consists mainly of eosinophils, though neutrophils are also present and these may be particularly dense if there is a concurrent infection. Goblet cells in the submucosa are increased in number and there are islands of epithelial regeneration. If the disease is long-standing the basement membrane becomes thickened and the smooth muscle surrounding the bronchi increases in thickness. Edema and vessel dilatation are also present.

Recent radioimmunological studies of the thickened bronchiolar basement membrane have detected granular deposits of immunoglobulins, particularly IgM and IgA; complement was also detected in a few cases. IgE was not detected however. Similar studies in controls showed no basement membrane thickening, but fluorescence with antiserum to IgG and IgM was seen occasionally. Callerame et al[2] feel that these deposits represent precipitation of antibodies from the serum with respiratory antigens from the bronchial lumen. Other studies have concluded that the differences between asthmatic and normal bronchial tissue deposits are not so clear-cut, and that immunoglobulin deposits are a non-specific finding. In summary then, it can be said at present that while pathological studies are suggestive of an immunological process, in themselves they are not conclusive.

ETIOLOGY

Immunological Aspects – It has long been recognized that asthmatic children frequently suffer from such aller-

gic conditions as hay fever and that individual attacks could sometimes be attributed to such allergenic substances as dust or pollen. Moreover, as shown above, the pathological picture in asthma shows allergic features. To be more conclusive, however, biochemical evidence was needed.

Historically asthma has been linked to the reaginic type of hypersensitivity. In this reaction, a specialized class of antibodies, called reagins, is produced after a first exposure to antigen that has an affinity for certain target cells and coats their surface. After a second injection of antigen occurs, an antigen-antibody combination takes place on the surface of these passively sensitized cells setting off a biochemical sequence which leads eventually to the release of histamine and other mediators. Although histamine, 5-hydroxytryptamine, slow reacting substance A, kinins and prostaglandins have been shown in in vitro systems to be released by antigen-antibody complexes, conclusive evidence of their role in atopic diseases is not yet available.

The most significant advance in this area has been the identification of the reaginic antibody. In 1966 Ishizaka and Ishizaka isolated a serum protein from the sera of atopic patients which had reaginic activity. It was later shown to be an immunoglobulin distinct from the classes then extant and was designated IgE[3]. The molecule was shown to be susceptible to cleavage by papain and pepsin, meaning that it consists of two light and two heavy polypeptide chains. IgE has a molecular weight of 200,000, a sedimentation coefficient of 8·2 S, and a half life of 2 days (implying that it is in continuous production). The serum concentration of IgE in normal individuals is very low, about 0.1 - 0.7 ug/ml. Rowe & Woods[4] have recently measured IgE levels in asthmatic and normal children but could not find a definite correlation between raised IgE levels and disease. Many atopic patients had levels of antibody well within the normal levels. But Ishizaka has demonstrated plasma cells producing IgE in the upper and lower respiratory tract, suggesting that it is local production rather than overall serum levels that is a factor in the pathogenesis of hay fever and asthma. Furthermore, circulating basophils in atopic patients have a coating of IgE on their membranes suggesting that these cells act as a transport system to the target cells.

Until recently delayed hypersensitivity was believed to play no part in atopic disease. In this process, tissue damage is caused by specifically "allergized" cells reacting with the antigen, serum antibodies are not employed. Intradermal injections of antigen in atopic subjects produces a reaction that differs in appearance and time course from that seen characteristically in delayed hypersensitivity. Moreover the pathological picture in asthma does not show any granulomatous features. However Brostoff & Roitt[5] in 1969, using in vitro techniques, demonstrated the presence of antigen specific lymphocytes in summer hay fever.

To reconcile these isolated findings with the non-granulomatous picture in asthma, Brostoff & Roitt invoked the hypothesis of cell-cooperation. The lymphocytes involved in delayed hypersensitivity and those that differentiate into cells involved in humoral antibody production arise from a common bone marrow precursor cell but come to be immunologically separate. The former come to be marked by passage through the thymus (and are called T lymphocytes) whereas the latter do not (and are called B lymphocytes). It has been suggested that before the B lymphocytes can differentiate into cells that can produce humoral antibody they require the co-operation of or intimate contact with T lymphocytes. Thus the presence of T lymphocytes in conditions whose symptoms are produced by IgE interactions with allergens can be explained. While the full roll of allergic mechanisms in asthma has not yet been elucidated, it is clearly more complex than was previously believed.

PSYCHOGENIC ASPECTS

In approaching this topic, it is important to differentiate its two aspects: first the ability of psychological stresses per se to produce an asthmatic attack, and second their ability to modify or exacerbate pre-existing etiological factors. The pathologic and biochemical evidence clearly indicates that it is an immune process that initiates the clinical syndrome of asthma in most cases, especially in children. It is equally clear though, that the frequency of subsequent attacks is not solely a function of the number of exposures to the original sensitizing antigen(s) and that psychological stress can be a major and in some cases dominating factor. It is clinically important because it is often the only factor that is remediable.

Many commentators have noted how emotional excitement can affect the frequency and severity of asthmatic attacks. The most famous example occurred just before World War II. A number of asthmatic Dutch children were sent to boarding school in a town in Switzerland. The Swiss observed that the school was more beneficial for the Dutch children than local children. After the war the Dutch established a central boarding school of their own and obtained equally good results. In both cases, attacks were more frequent on visiting days, and just before holidays. Recent quantitative studies have indicated that changes in pulmonary function tests due to inhalation of standard amounts of allergen varied depending upon the emotional state of the subject (which was varied by the occasional insertions of data from the subjects' personal histories).[6]

Some psychiatrists have attempted to characterize the personality of the asthmatic in order to explain his susceptibility to respiratory problems. Some have found asthmatics to be more anxious, sensitive, and obsessional than controls. Many psychoanalytic theories have been advanced about its dynamics, the most common being

that the essential conflict in the patient is his repression of crying for fear of maternal rejection coupled with unconscious impulses to leave her in the face of his strong attachment to her. All these psychiatric studies are limited because they are necessarily retrospective; the patients they see have had a chronic illness often for several years previously, one that does not smoulder, but proceeds via a repetitive series of severe acute episodes that temporarily render their victim totally dependent on others. That is not a healthy situation, and surely one that shapes the patients' behaviour towards anxiety and obsessionality.

Behaviorist research has perhaps been most useful. It has demonstrated that suggestion and conditioning as well as anxiety can exacerbate asthmatic attacks. Experimenters have been able to induce asthma-like states in animals by both classical and operant conditioning techniques and these may eventually be applied to man. Luparello[7] found that asthmatic subjects inhaling nebulized saline reacted with increased airway resistance when told that it was an allergen to which they were sensitive. In this experiment suggestion as well as anxiety was involved.

These experiments have important implications in management. Due to the periodic, repetitive sequence of events in asthmatic attacks, accompanied by routine and often ritualized forms of drug therapy, a series of cues are reinforced in the patient's mind, causing a form of "stimulus generalization", lowering the effectiveness of therapy, and progressively increasing the patient's anxiety, which in turn intensifies the severity of subsequent attacks. Simple psychotherapy can help break the circle down. Intensive psychotherapy is often not needed. Similarly if those situations that are particularly stressful to the patient are identified, they can then be dealt with more successfully. Complex formulations are not needed.

PATHOGENESIS

Traditionally the anaphylactic guinea pig has been used as the model to describe the pathogenesis of asthma. It has been discarded because it does not explain many of the features seen in asthmatic attacks, and replaced as a model by mice suffering from Bordatella pertussis. These animals, unlike the anaphylactic guinea pigs, are hyperactive not only to histamine but to less specific stimuli, produce a reaginic antibody response, show a marked eosinophilia, and a reduced susceptibility to catecholamines. All are features of human asthmatic attacks.

Using these mice Szentivanyi determined that their hyperactivity is due to an imbalance of their two adrenergic receptor systems. With his associates he found that if peripheral glucose uptake is inhibited by deficient beta adrenergic activity, then the tissues are more reactive to histamine. He then extrapolated these results to man.[8] His hypothesis is that histamine and other mediators are natural chemical organizers of autonomic action. (Histamine and the other mediators are unleashed by the infective and psychogenic causes as well as the immunological in his hypothesis.) Response to their action requires activation of their antagonists, the catecholamines, and their expression in a balanced system of the two adrenergic receptors and their target organs. The asthmatic possesses a genetic or acquired block on the beta side so that alpha activity is unopposed; in the bronchial tree that would result in generalized constriction.

If this hypothesis is true it would mean that the intrinsic and extrinsic types of asthma, while differing in etiology have a common pathogenesis. While this is attractive there is no unanimity on the subject at the moment.

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The Significance of Metabolic Patterns in the Lung

Dorothy Miller, B.Sc.

Recent studies on lung biochemistry have demonstrated that the lungs can no longer be considered as just an elaborate pair of bellows or a bag for passive gas exchange. They are an extremely active metabolic organ and are involved in a wide variety of synthetic and degradative reactions. Some of these processes, like the synthesis of surfactant, are essential to normal respiratory function; while the metabolism of hormones, steroids and drugs, may be an integral part of the regulatory mechanisms of the body. My aim is not to discuss any of these topics in detail; but simply to emphasize the scope of the processes involved, and some of the implications these have for clinical medicine.

The alveolar level of pulmonary tissue is my chief concern and here, three basic cell types are present; the alveolar macrophage, the membranous pneumonocyte or Type I alveolar cell, and the granular pneumonocyte or Type II cell.[1]

The alveolar macrophage will not be dealt with in this article but it undoubtedly has unique metabolic capacities which promote the phagocytosis and elimination of foreign elements.

The Type I cells are flattened epithelial cells of the alveolar wall with long, thin cytoplasmic extensions and few mitochondria. No specific function has been attributed to these cells but they may be involved in the rapid diffusion of gases between blood and air.

The Type II cells are the major metabolic components of the lung parenchyma and contain an abundance of enzymes active in the Krebs cycle and in lipid biosynthesis. They are rounded cells interspersed between Type I cells and contain a characteristic granular cytoplasm and well-developed endoplasmic reticulum. These cells undergo continuing renewal, and proliferation of this population may be part of the normal defense mechanism of the body.[2]

SURFACTANT[1] [2]

One of the lung's most important functions is the synthesis and secretion of the surface-active material, surfactant, which is essential to normal pulmonary function and lung viability. Surfactant is believed to form a complete lining layer over the alveolar surfaces and be the major determinant of the elastic properties of the lung. It produces a surface tension which varies directly with surface area so that significant volumes can be maintained in the alveoli at low pressures.

The exact composition of surfactant is not known but it may be essentially a phospholipid-protein complex, which is synthesized by the microsomal and mitochondrial fractions of the Type II alveolar cell and stored in the "osmophilic" inclusion bodies of these cells until it is secreted into the alveolus.[3] The major phospholipid component is dipalmitoyl lecithin and it is the prime contributor to the surface activity of surfactant.

Recent studies have shown that surfactant has a rapid turnover rate and that the active lipid metabolism demonstrated in the lung may be vital for the continuous replacement of the lining. Uptake and hydrolysis of circulating lipids by the lung is very efficient and the free fatty acids, acetate, and palmitic acid are preferentially incorporated into phospholipids. In this capacity alveolar cells are insulin resistant and show a higher synthetic ability than hepatocytes.[1] The pathway for the synthesis of dipalmitoyl lecithin involves l-α-glycerophosphate and CDP-choline but a minor pathway utilizes the N-methyl transferase reaction.

In light of the importance of the surfactant system to normal pulmonary function and the requirement for rapid phospholipid synthesis, it seems reasonable that any increase in the destruction of surfactant, or any impairment of the synthetic process could lead to surfactant deficiency. Despite the fact that this specific deficiency has never been firmly established as an etiological factor, it may play an important role in the manifestations of pulmonary disease. For example, many noxious airborne substances are capable of altering the surfactant system.

Both inhalation of ozone and prolonged oxygen administration result in morphological alterations in the alveolar macrophages causing cell lysis and finally pulmonary edema. In the absence of edema, there is no change in the pulmonary surface activity and it must be concluded that surfactant is not directly involved in the lipid peroxidation which causes cell injury.[4] Similarly NO_2 is an oxidant which has been shown to cause lipid peroxidation at points of unsaturation in cell membranes. In this case the endothelial cell seems to be the primary site of injury, and only after the formation of edema does the surface activity of the alveoli change.[5] Although the above mentioned compounds have no direct effect on surfactant, the subsequent alteration of its properties may enhance the severity of the lesion by increasing pulmonary edema and producing atelectasis.

RESPIRATORY DISTRESS SYNDROME

One of the best known diseases related to surfactant deficiency is the respiratory distress syndrome of the newborn. Observations that the major clinical aspect of this disease was massive alveolar collapse, pulmonary instability and abnormal surface tension properties, strongly implicated the surface-active lining layer in the etiology.

In the normal fetal lung, at about the fourth month, the cuboidal or columnar cells of the terminal lung units

begin to differentiate and, by the sixth month, two distinct cell types may be recognized: Type I cells with long cytoplasmic extensions, and Type II cells with large intracellular inclusion granules. The presence of normal surface activity correlates well with the appearance of Type II inclusion bodies and a significant increase in dipalmitoyl lecithin content of the lungs for most species.[6] During development, the fetal lung is filled with pulmonary fluid, which is synthesized by the lung tissue, and exhibits normal surface tension properties. At birth, an air-filled lung takes over quickly. The pulmonary fluid is rapidly cleared from the lung by absorption into the blood stream, and a surface-lining layer is formed from small amounts of pulmonary fluid and secretions of Type II cells. The quantitative and qualitative aspects of these two components may be of the utmost importance in establishing and maintaining alveolar wall integrity and lung stability in the immediate post-natal period. Since the respiratory distress syndrome is associated with pregnancies involving maternal diabetes, premature delivery, and complications with fetal distress, the inhibited maturation of the surfactant system may represent the initial defect.

Studies on the maturation of this system in sheep have revealed that fetal asphyxia due to impaired blood flow to the fetus caused significant reductions in pulmonary synthesis of dipalmitoyl lecithin.[6] By infusion of a normal fetal twin lamb with cortisone and hydrocortisone, significant stimulation of lung maturation was observed.[7] Other workers, using rabbits and fluprednisolone found a similar stimulation of lung maturation, an increase in the number of Type II alveolar cells, and an increase in the synthesis of dipalmitoyl lecithin.[7] Despite the fact that biochemistry and regulatory controls of surfactant in the human have not been established, the presented evidence suggests that a deficiency of surfactant is a major factor in the etiology. If this is the case, corticosteroids may be useful in the mitigation of the disease.

VASO-ACTIVE HORMONES[8]

Although the production of surfactant is an essential function, the metabolic capacity of the lungs includes several other areas. The lungs have a very important role in the selective metabolism of circulating hormones, especially vaso-active substances.[9] Vaso-active amines such as acetylcholine and serotonin are completely removed by the lung in one passage through the pulmonary circulation. Noradrenaline is only partially removed, while adrenaline and histamine are not altered. Bradykinin and some prostaglandins are completely cleared from the blood while oxytocin and vasopressin pass through the lungs unaffected. It appears that any hormone which circulates in the blood stream and has a generalized physiological function is not destroyed by the lungs, but a "local" hormone, whose action is probably localized at or near the site of release, is completely cleared before it can reach the arterial circulation. The significance of this phenomena will be illustrated by a discussion of bradykinin and prostaglandin inactivation.

Bradykinin is a powerful vasodilator and increases capillary permeability. It is produced in the blood by the activation of plasma kininogenase during an inflammatory response and is cleared almost completely in one passage through the lung. Using radioactive bradykinin, the inactivation occurs extremely rapidly through hydrolysis of peptide bonds, and there is some evidence that the lung enzymes are located on or near the vascular endothelium.[10] Under normal conditions very little bradykinin would be expected to reach the arterial circulation; but if the amounts of kinins released were very large, or the kinin-cleaving enzyme was defected or inhibited, these pathological states would become evident.

In particular, the flushing episodes with carcinoid tumor metastases and the dumping syndrome have been correlated with elevated kinin levels in the blood.[11] The carcinoid tumor contains a kininogenase which produces a bradykinin-like peptide, and this peptide is responsible for the ensuing bronchoconstriction, vasodilatation and hypotension. The dumping syndrome is a common complication of gastric surgery, and the flushing episodes, which accompany it, have been attributed to serotonin released from the intestines. However, it is now believed that there is a release of bradykinin-like activity into the blood which correlates with the flushing phase, while no such correlation is seen with blood levels of serotonin. In these two cases, kinin levels may exceed the levels which the lung can effectively clear; or there is in addition a kinin potentiating factor involved. Some factors have been isolated from the venom of a Brazilian snake which inhibit the kinin-cleaving enzyme of the lung and potentiate the action of bradykinin in vivo as well as in vitro.[12] An excess of bradykinin may also play a significant role in the pathogenesis of emphysema by causing bronchiolar constriction, pulmonary edema, and increased capillary permeability.[9]

Prostaglandins are another example of biological activity which is regulated almost entirely by the lung.[13] Prostaglandins are lipoid substances which have potent effects on vascular and intestinal smooth muscle. These compounds are released from very diverse areas of the body including the cerebellum, adipose tissue, adrenal gland, and spleen by nervous and adrenaline stimulation. The lung is also capable of secreting prostaglandins. Prostaglandin E_2 was identified as being released by the lung in response to inflation and may contribute to the hypotension which accompanies positive pressure ventilation.[14] This same prostaglandin is also released during anaphylaxis in association with histamine and other vaso-active substances.[8] Prostaglandin E_2 has also been implicated in the haemodynamic effects of pulmonary embolism in man – "colloid shock" with hypotension, hyperventilation and broncospasm.[15]

Both the liver and lung are major sites of removal of these substances, but the lung is slightly more active.

Enzymes which metabolize prostaglandins, such as 15-hydroxy-prostaglandin dehydrogenase and prostaglandin-12, 13-reductase, can be extracted from the lungs of many species and the pulmonary removal of prostaglandins may be enzymatic inactivation.[16] Not all prostaglandins are cleared in the lung and, since prostaglandin A passes through unaltered, it may be a circulatory hormone in the regulation of renal function.[9] The lungs possess a highly efficient mechanism for inactivating prostaglandins and an ability to secrete prostaglandin E_2, so that they seem uniquely equipped to regulate the prostaglandin concentration in arterial blood. If they do in fact exert such a control, it might be significant in the regulation of systemic arterial blood pressure.[14]

Angiotensin II is the pharmacologically active component of the renin-angiotensin system and its formation was found to take place exclusively in the lung.[17] The converting enzyme appears to be localized in or on the capillary endothelial wall in direct contact with the blood and is capable of almost complete clearance of Angiotensin I. The discovery of this crucial converting enzyme provides a key to the pharmacological study of the renin system. Any disruption of alveolar structure or biochemistry, or inhibition of the enzyme would greatly impair the biological activity of the system.

STEROID METABOLISM

Despite the impressive metabolic activity of the lung already described, the pulmonary tissue is involved in at least two more important aspects of body metabolism. It has been well established that non-endocrine tissue also participates in general metabolism of steroid hormones. The lung is active in this regard but the quantity and quality of this system are not known.[18] From an infusion of 7-α-^{3}H-dehydroepiandrosterone ^{35}S-sulfate into the human lungs, major metabolites such an androstenediol, testosterone, and androstenedione were identified. Small amounts of estrogens were also formed but no conjugated steroids were detected. At this stage of knowledge, it is difficult to assess the significance of this finding; but there are old reports in the literature which point out an association of pulmonary disease with gynecomastia.[19] In particular, Brambilla reported that a four-year-old girl experienced periodic episodes of mammary enlargement and slight genital precocity during attacks of mild respiratory infection. Therefore, in spite of the low level of steroid metabolism in the lung, there are indications that changes in pulmonary biochemistry can be extreme enough to produce pathological situations.

DETOXIFICATION OF FOREIGN COMPOUNDS[20]

Detoxification of foreign compounds is another important function which has recently been associated with the lung. The liver is the primary site of drug metabolism and the mixed function oxidases attached to the endoplasmic reticulum are the major enzymes involved. A similar inducible but small population of these enzymes have been discovered in the lungs probably in association with the well-developed endoplasmic reticulum of the Type II cells. The characteristic inducers of the liver enzymes such as phenobarbital do not affect the lung enzymes significantly but 3-methylcholanthrene, chlorpromazine, and phenothiazine do increase the enzyme activity in some species.[21] Evidence now exists for the presence of cytochrome P_{450}, NADPH and NADH cytochrome c reductase, aniline hydroxylase,[22] aminopyrine demethylase,[21] amino azo dye N-demethylase,[23] and benzapyrene hydroxylase in the lung. Both lung and liver mixed function oxidase systems are inhibited by cytochrome c, SKF 525A, and CO.

Despite the low activities observed for the lung, any changes in these enzyme levels at or near the receptor site may alter the pharmacological actions of the foreign compounds involved and mediate an effective regulatory control.[23]

Perhaps one of the significant findings is that benzapyrene hydroxylase occurs in the lung. Benzapyrene is a major carcinogenic ingredient of tobacco smoke, and the presence of its detoxifying enzyme in the lung may represent part of a protective system against environmental carcinogens. Under normal conditions the enzyme activity is too low to detect, but its activity can be induced by several compounds as well as benzapyrene itself. The actual mechanism of carcinogenicity of benzapyrene in rat lungs has been studied.[24] It appears that metabolic activation is a prerequisite for covalent binding of polycyclic hydrocarbons to cellular components and DNA. This metabolic activation correlates well with carcinogenicity and cytotoxicity. Preliminary evidence suggests that hydroxylation of benzapyrene and the binding of benzapyrene to DNA may be separate functions but with a common initial step involving microsomal enzymes, NADPH and O_2. In addition it may be possible to encourage the production of relatively less toxic hydroxylated products while inhibiting the binding to biologically important molecules. Theoretically, it should be possible by using suitable enzyme inducers prophylactically to protect people from environmental carcinogens. With high levels of benzapyrene hydroxylase in lung tissue humans may become less susceptible.[20]

The studies on the metabolic patterns of the lung have just begun and the application of the findings, presented here from various animal systems, to man is speculative. In addition the clinical importance of these patterns is even more obscure. There can be little doubt, however, that the lungs exert a very specific and important regulation of our internal environment quite apart from their ventilatory function.

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Review Of Streptococcal Pharyngitis

Patricia Clifford, 7T2

Pharyngitis is inflammation of the pharynx including tonsillitis. The agent of particular concern among the causes of pharyngitis is the Group A beta-hemolytic streptococcus. This microorganism is associated with much morbidity in children and adults. Besides the actual infection, which accounts for 1 out of 20 children visits to doctors on this continent[1], the streptococcus is associated with the immediate complications of pharyngeal wall abscess, sinusitis, otitis media, mastoiditis, temporal lobe abscess, and meningitis. The late complications include acute rheumatic fever and acute glomerulonephritis. It has been estimated that 0.33% of untreated cases of streptococcal pharyngitis go on to acute rheumatic fever; 0.17% to acute glomerulonephritis[2]. Or to look at the problem from another angle, in diagnosed cases of acute rheumatic fever as suggested in an article from the Pediatric Journal[3], 27% of patients could cite a streptococcal illness for which they had not consulted a doctor and 24% had seen a physician who failed to recognize or improperly treated streptococcal pharyngitis.

The problem could be attacked by treating every pharyngitis with penicillin which is still the drug of choice. However, not only is an injustice done to the patient without streptococcal pharyngitis with regard to cost of the drug and subjecting him or her to the risk of toxic reaction; but also, if a specific diagnosis is not attempted, other possibly fatal diseases may be missed. So it is worth the effort to learn if and how the various agents causing pharyngitis can be differentiated.

Normally the pharynx is inhabited by several non-pathogenic and in some people pathogenic micro - organisms. The former group includes alpha-hemolytic and non-hemolytic streptococci, Staphylococcus albus, Neisseria, diphtheroids, spirochaetes, fusiform bacilli, Bacteroides, mycoplasma, candida and actinomyces species. The latter group includes beta-hemolytic streptococci, pneumococcus and Hemophilus species. Since not all cases of pharyngitis have confirmed causative agents, the micro-organisms may be re-classified in future; for example, Mycoplasma.

The methods for identifying the infectious agents include essentially the culture of the organism from throat swabs onto various media and the monitoring of antibody levels during the illness. For identifying beta-hemolytic streptococcus, a study reported in the American Journal of the Diseases of Children[4] used cultures from throat swabs and a rise in ASO titres. They found that where physicians were definitely sure of a diagnosis of streptococcal pharyngitis, the cultures were 78% positive. A significant rise in ASO titre was not found in all of these cases. As well, in patients with negative cultures for streptococcus, no significant ASO titres were found. Therefore, the culture is the more trustworthy method of diagnosing a streptococcal infection.

However, Stillerman and Bernstein[4] found that single throat cultures were associated with two sources of error, 3% from false positives or false negatives and 13% from carriers of streptococcus. Throat culture remains a reliable method of checking the diagnosis of streptococcal pharyngitis bearing in mind its limitations.

The problem, however, is whether positive cultures are needed to make a diagnosis of streptococcal pharyngitis or can a physician decide with confidence which acutely inflamed throats are caused by beta-hemolytic streptococci.

Pharyngitis can be a feature of systemic as well as upper respiratory tract disease. The former includes infectious mononucleosis, agranulocytosis and leukemia, although the sore throat in leukemia and agranulocytosis is probably caused by local infection.[5] The agents implicated in primary upper respiratory tract infection with pharyngitis include: the bacteria, Group A beta - hemolytic streptococci and Corynebacterium diphtheriae; Mycoplasma; the viruses, rhinovirus, adenovirus, coxsackievirus, ECHO and herpes viruses, respiratory syncitial virus, mumps, influenza and parainfluenza viruses; and finally, the fungus Candida albicans.

If the patient has not been or is not generally well, or has generalized lymphadenopathy or splenomegaly, the primary blood disorders should be seriously considered. A peripheral blood smear with white blood cell count and differential are indicated. The leukemic may complain of bone pain or have evidence of infection elsewhere especially around the gingiva. There may be an epidemic of infectious mononucleosis in the community. Heterophile antibody may help make this diagnosis.

Cough, hoarseness, nasal discharge or conjunctivitis, that is, any common cold symptom, suggests a viral agent, probably rhinovirus. The accuracy of diagnosis using these symptoms is close to 100% in most studies reported.

Corynebacterium diphtheriae is associated with a grey membranous exudate on the tonsils and pharyngeal walls. However, diphtheria should be suspected if any membrane is present, especially if there is bleeding on trying to remove it. The membrane can extend down the respiratory tree causing obstruction or may at times extend through the external nares. The exotoxin produced by the bacteria affects peripheral nerves causing paralysis. This may be manifested at first by regurgitation of liquids through the nose due to palatal paralysis. Generalized paralysis is the final outcome. Circulatory failure also is common. Corynebacteria are cultured on Loeffler's slant or tellurite medium. It is important that patients suspected strongly of having diphtheria should be treated immediately with diphtheria antitoxin.

Candida albicans usually produces white exudates on the tonsils and pharynx but also on the buccal mucosa.

However, it can be confused with diphtheria if the exudates coalesce. Candida infection is often connected with the taking of broad-spectrum antibiotics like tetracycline.

The clinical presentations of the many other organisms that can cause pharyngitis overlap a great deal. There are, however, some helpful clues to diagnosis.

First of all, the age of the patient may point to the causative agent. Acute pharyngitis is uncommon in infants less than one year of age. Perhaps these babies aren't attacked by pathogens because of their relatively sheltered environment or because the doctor misses a mildly inflammed throat in the "cranky" baby. More likely, the baby produces a generalized reaction to the invading micro-organism, a reaction which later in life localizes to the throat as the child's immunologic and cellular defence systems mature and start to respond. This is further illustrated by the fact that the signs and symptoms of streptococcal infection become characteristic over the age of four.[4]

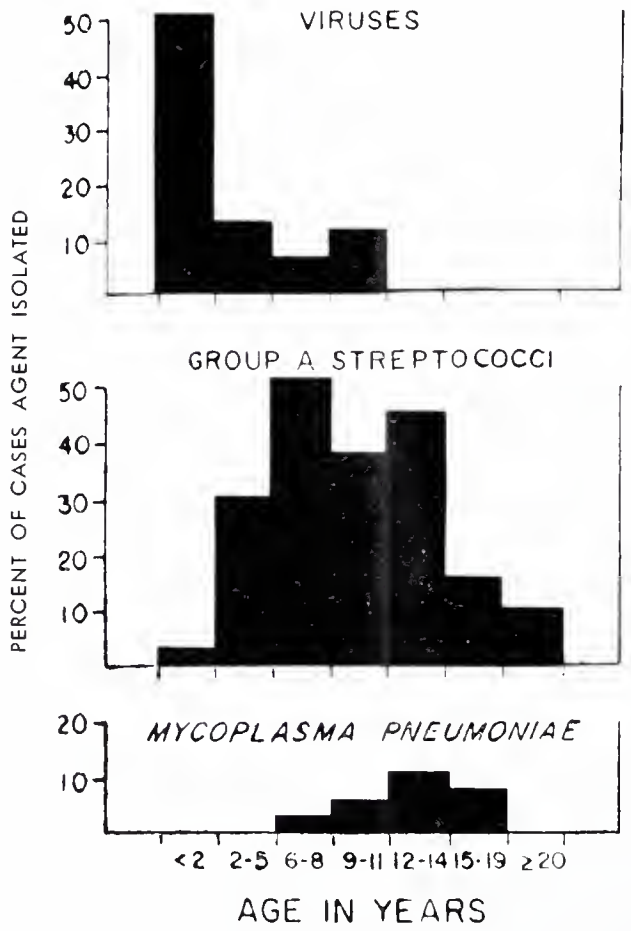

FIG. 1: Recovery of microbial agents from persons with pharyngitis, by age.

Infants under two years of age with the diagnosis of pharyngitis are infected with a virus in the majority of cases as illustrated in figure 1. The figure also illustrates that between 2 and 14 years of age, streptococcus is the major cause of pharyngitis, with a peak incidence at 6 to 8 years of age. Mycoplasma reaches its peak between 12 and 14 years; however, it was a rare cause of pharyngitis in the total survey. The children accepted for this study[6] had exudative pharyngitis, non-exudative pharyngitis with cervical lymphadenopathy, scarlet fever or any complaint of sore throat during streptococcal epidemics. The viruses isolated a significant number of times were adenovirus and parainfluenza virus types 1, 2, 3. The picorna viruses and herpes virus were not. These investigators did not culture for respiratory syncitial virus nor influenza virus. Their findings do not agree with other clinical surveys. For example, in a study by Moffet et al[7], the significant viral pathogens found included adenovirus, herpes virus and coxsackie A virus. ECHO and type B coxsackie viruses were not found commonly. The patients accepted for this group had to have erythema, exudate or ulcerations of the pharynx or tonsils. Also they had either fever or exudate and could not have gingivitis, glossitis nor stomatitis. This study found Candida also in a significant number of cases. Besides streptococcus, bacteria could not be proven to be causes of pharyngitis. Of particular interest were Staphylococcus aureus and pneumococcus.

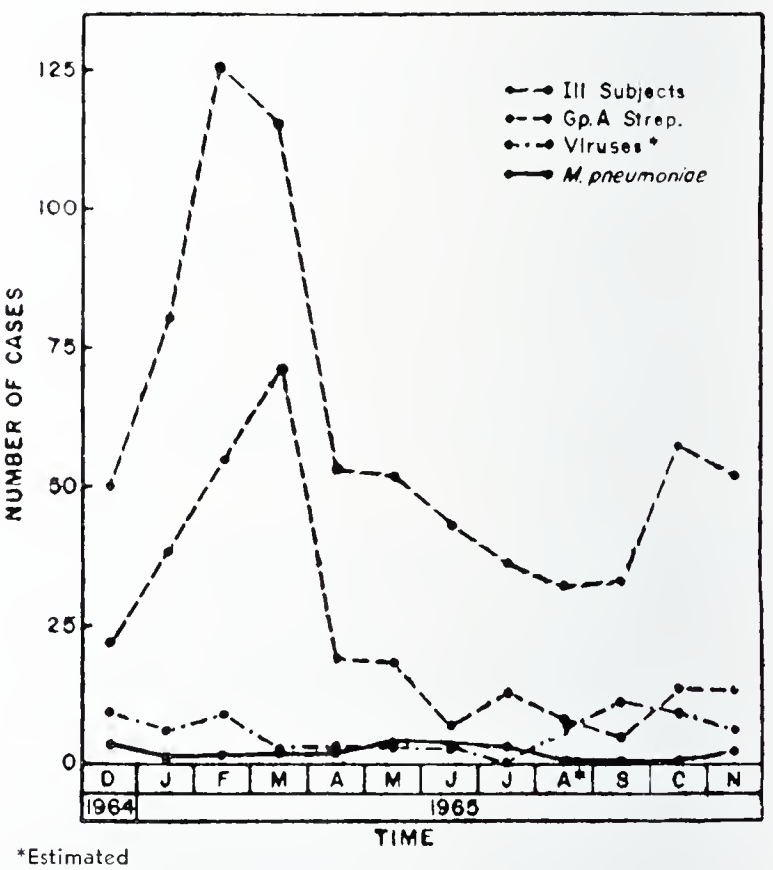

FIG. 2: Isolation by month of group A streptococci, viruses and *M pneumoniae*.

(From Glezen et al: "Group A Streptococci Mysoplasmas and Viruses associated with Acute Pharyngitis". Jama 202:455, 1967.)

Another clue to the etiological agent is the season of the year, as illustrated in figure 2. The streptococcus peak was in February and March which coincides with the peak incidence of pharyngitis during the year. It can be seen that the number of cases caused by other micro-organisms varies little during the year. Also of note is that no greater than 50% of cases at any one time have a causative agent isolated. Which known and unknown pathogens are we failing to recognize?

So the most common known causes of pharyngitis are the Group A beta-hemolytic streptococcus and various viruses. Can these two groups be recognized from clinical information?

A classical viral pharyngitis is gradual in onset and lasts from one to five days. Fever, malaise and anorexia early are followed by mild sore throat which reaches peak severity about the second or third day. As mentioned above, cough, hoarseness, rhinitis, and conjunctivitis are common. On examination, the pharynx is usually mildly erythematous but may be severely red. Ulcers on the soft palate are associated with viruses, especially Coxsackie A, and exudates may be present. The servical lymph nodes are moderately enlarged and may or may not be tender.

Streptococcal pharyngitis is sudden in onset and may last up to two weeks. Headache, abdominal pain, vomiting and fever up to 104°F occur in the first twelve hours. This is followed within hours by mild to severe sore throat. On examination definite erythema occurs in two-thirds. The tonsils are generally enlarged and with exudates. A combination of these three signs occurs in one-third of patients. Cervical lymph nodes are enlarged and tender. Very rarely is there conjunctivitis, rhinitis, cough or horseness.

I should mention that the removal of tonsils does not prevent a child from getting pharyngitis.

Clinical studies have been reported concerning the ability of experienced physicians to diagnose streptococcal pharyngitis by using these clinical syndromes. Smith, D.D. et al[8] compiled a series of 199 cases where pharyngitis was diagnosed as streptococcal or viral, the signs and symptoms used to make the diagnoses were recorded. The diagnoses were checked by culture for streptococci. 95 cases were diagnosed as streptococcal, of which 33% has positive cultures. 104 cases were diagnosed as non-streptococcal and of these 6% had positive cultures, which agrees with a carrier rate only. Coryza was their only indication for viral pharyngitis; fever exudate and swollen glands, for streptococcal pharyngitis. It seems that physicians can have confidence in that what they say is non-streptococcal is just that. However, in this case streptococcal pharyngitis was over-diagnosed.

Stillerman and Bernstein[4] analyzed a series of 1141 cases of pharyngitis in a similar manner. They found 78% positive cultures on patients diagnosed as definite streptococcal pharyngitis, 38% positive cultures in equivocal cases, and 14% positive cultures on definite non streptococcal pharyngitis, which agreed with their carrier rate. These people then under-diagnosed. Their criteria for distinguishing the causes of pharyngitis were more elaborate. Fever, sore throat, headache and gastrointestinal complaints without cough were considered indicative of streptococci. Cough and hoarseness indicated a viral organism. Redness and edema of the oropharynx, exudate on the tonsils, red stippling or petechiae on the soft palate, and anterior cervical adenitis were used to indicate streptococci.

Next they analyzed the reliability of individual signs and groups of symptoms and signs in diagnosis.

Petechiae on the soft palate had the highest percent of positive cultures; in fact, a ten to one ratio in favour of streptococcal disease. However, this sign occurred in approximately 7% of cases only. Scarlatinal occurred in a ratio of thirty-nine to one for streptococcus but only in 4% of the total cases. Therefore these two signs although of high reliability are not helpful because of their low incidence. Over-all, marked redness of the pharynx was the most useful diagnostic sign with 77% positive cultures and an incidence of about 35%. Exudates on the tonsils and cervical adenitis have positive cultures at a rate of 65 and 61% respectively but with a lower incidence than that of marked redness.

Generally, combinations of these characteristic signs were found to be better indicators of streptococcal pharyngitis. The following syndromes were associated with more than 70% positive cultures:

1. Moderate redness or edema, moderate or marked exudate, adenitis 75%
2. Marked redness, with or without exudate, with or without adenitis 74%
3. Moderate or marked redness, moderate or marked petechiae, with or without adenitis 95%
4. Moderate or marked redness, exudate, petechiae and with or without adenitis 100%

72% of patients without cough and with fever, sore throat, headache and gastrointestinal complaints had streptococcal disease by culture.

SUMMARY

In summary, then, if a child of seven years of age comes into your office in March complaining of a sudden onset of fever, headache, sore throat and upset stomach without cough or coryza, and you find on examination a markedly inflammed throat, he or she is very likely to have streptococcal pharyngitis.

The following questions shall remain to be answered. Does one wait for a positive throat culture or start treating immediately a suspected streptococcal disease? Will a delay in treatment increase the child's risk of complications if he or she has streptococcal disease? Does treatment prevent these complications?

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Intrauterine Respiration Of The Human Fetus In Relation To The First Breath

Wayne Quan, 7T2

Profound adjustments and changes occur within the days or even hours following birth. Studies of the changes that occur are extremely important because more infants die within the first year of life than in any other period of life.

Of the many almost instantaneous adaptations that a newborn infant must make, those involving respiratory and circulatory adjustments must start within minutes after birth. The gas exchange that was formerly performed by the placenta must be taken over by the lungs. The key mechanism involved in this adaptive process is the onset of breathing and aeration of the lungs.

There has been much controversy as to when respiration actually begins – whether respiratory movements are a continuation of intrauterine respiration or initiated at birth. Rhythmic thoracic movements have been observed in many laboratory fetuses and also in human fetuses. In fact, respiratory movements in the fetus were well established by observers as early as Versalius. The question is whether these movements are a normal physiological part of intrauterine life. If so, then respiration after birth is merely a resumption of intra-uterine respiratory movements. This offers a simple account of the onset of respiration after parturition.

Some observers, however, have been unable to see intra-uterine respiratory movements. This may be due, in part, to the fact that maternal anaesthesia was used which caused cessation of fetal movements. Even so, there is an irregularity in the appearance of intrauterine respiratory movements. The fact remains, however, that since infants of 600 grams at birth have survived and displayed sequential gasps, it is evident that the human neural regulatory apparatus can initiate and sustain respiratory activity early in fetal development.

Further unequivocal evidence that fetal respiration does occur can be obtained through the injection of radiopaque or dye materials into the amniotic sac and through the later search for the injected material in the fetal lung. However, these respiratory movements are not sustained rhythmic respirations throughout gestation. They occur infrequently and are subject to alteration by many factors. The use of anaesthesia suppresses them and this may account for the infrequency of their observation by many individuals.

A study of intrauterine respiratory movements was made by Snyder and Rosenfeld in 1936 without the use of anaesthetics and with the inhibition of labour. They inhibited labour in a rabbit with an intravenous injection of urine extract from pregnant rats. This injection was administered one week before the end of the normal gestation period. To eliminate the need for anaesthesia, they sectioned the spinal cord at the level of the second lumbar vertebra. By this procedure the authors were able to perform laparatomy without the use of general anaesthesia.

Exposure of the fetus from the peritoneal cavity was done beneath the surface of a 37°C Ringer solution bath. The translucency of the rabbit uterine wall and the virtual absence of amniotic fluid permitted clear vision of any movements of the thorax and abdomen of the fetus.

In their observations, marked differences in the rate of breathing were observed, even among fetuses of the same litter. Some were seen to have respiratory movements of regular rhythm even though the other members of the litter were apneic. If, however, all the fetuses were removed from the uterus and placed in the open air, they all breathed with the characteristic newborn rhythm. Increased respiratory movements resulted when the fetuses were placed into the saline bath while the cord was still intact. Respiratory movements of apneic fetuses were initiated by such a procedure. The resultant rate was less than that of the newborn, however.

Characteristic maximum rates of respiration were observed for fetuses of various ages. A maximum intrauterine rate of 30 per minute was observed in the full term (32 days) fetuses. Those that were 30 days old showed a maximum rate of 15 per minute. Postmature fetuses of 34 days showed respiratory rates as high as 60 per minute. This is in contrast to the very rapid rate of 180 per minute in the newborn.

To ascertain whether the changes brought about by various concentrations of oxygen and carbon dioxide in the fetus had any relationship to the results observable in the postnatal animal, the effects of various blood gases on fetal respiratory movements were noted.

To test the effect of increased carbon dioxide on the respiratory movements of the fetus, the maternal animal was given a 7.5% carbon dioxide mixture. There was a marked increase in the rate of the maternal animal while the fetus exhibited little if any change. Only in some of those fetuses which had respiratory rates below the maximum characteristic of their age group showed an increase to the maximum rate upon the administration of carbon dioxide. Stimulation to a rate in excess of the maximum for a particular fetal age was impossible.

In contrast to carbon dioxide excess, a carbon dioxide deficit produced marked results. Forced hyperventilation of the maternal animal by artificial respiration at an increased rate and depth resulted in sharp decreases in the fetal rate within two minutes. This was followed by apnea which lasted several minutes before respiratory movements were resumed after cessation of artificial ventilation. Return to the normal respiratory rate was much slower in the fetus than in the maternal animal. As a

control, hyperventilation with a 5% carbon dioxide and oxygen mixture was performed, resulting in no depression of respiratory movements.

From the preceding observations, Snyder and Rosenfeld concluded that a specific level of carbon dioxide is required for the maintenance of fetal respiration even though an excess of carbon dioxide has virtually no effect.

A study of the effects of anoxemia dissociated from the complications of anaesthesia, parturition and mechanical stimulation was then made. While the maternal animal was subjected to a low oxygen gas mixture, a depressed fetal respiration was consistently observed. This effect was in contrast to the marked stimulation of respiration in the maternal animal. Respiratory movements were not initiated in quiescent fetuses by anoxemia.

Anoxemia could also be induced by obstructing the umbilical cord circulation. Depression of respiratory movements followed partial obstruction of the umbilical cord circulation. Respiratory movements were completely abolished upon complete obstruction. In apneic fetuses, however, sudden clamping resulted in several irregular gasps. When the fetal head was exposed to the air, clamping of the cord resulted in the establishment of pulmonary ventilation and an accelerated respiratory rate.

Fetal respiratory movements are profoundly influenced by general anaesthesia. Characteristic prolonged apnea before birth was observed in fetuses of anaesthetized maternal animals. Full-term rabbit fetuses exposed in a saline bath were found to be in a state of apnea if the maternal animal has been given pentobarbital sodium as a surgical anaesthesia. Thus the true physiological activity of fetal respiratory systems is masked by narcosis. Spontaneous respiratory movements were observed in fetuses of maternal animals under ether anaesthesia. Their respiratory movements occurred when the depth of anaesthesia was minimal. Therefore, anaesthesia may, in part, be the explanation for the negative observations of earlier experimenters in intrauterine respiration.

In concluding that intrauterine respiration does indeed occur, one must also conclude that respiratory movements are not initiated at birth. One must, therefore, go further back into embryonic life to discover when the first respiratory movement does occur.

The fetus very much resembles an adult animal that lacks a functional carotid body mechanism. In both, there is no stimulation of respiration following anoxemia. Instead there is an accentuation of respiratory depression under anoxemic conditions.

There is a qualitative similarity of the fetus to the adult response to carbon dioxide depletion even though the fetal respiratory centre is less sensitive than that of the adult. Apnea in both the fetus and the maternal animal was observed following hyperventilation by the mother.

Variations in the respiratory activity of different fetuses in the same litter was due to different degrees of anoxemia. Contraction of the uterine muscles results in impairment of circulation. This explains the regularity of fetal respiratory movements of fetuses in quiescent uteri under hormonal inhibition. In contrast to this is the irregularity of fetal movements in uninjected animals.

An increased oxygen supply could stimulate the respitory movements of apneic fetuses. Upon escape through a uterine incision, apneic fetuses begin respiratory movements upon contact with a saline bath. The increased respiratory movements evident at birth may be related to the new source of oxygen supply through the pulmonary ventilation. The introduction of a gas rather than fluid through the respiratory tract, increased peripheral stimuli of the external environment and the sudden alteration of the circulatory system may also be related to postnatal hyperpnea.

From the preceding, it seems possible that the stimulus for the onset of respiration at birth would more likely be of a chemical rather than a physical nature. Oxygen is a most likely candidate for the part.

An analysis of the oxygen content of the umbilical vein and of the umbilical arteries of sheep throughout the gestation period was made by Barcroft (1940). He discovered that the oxygen content varied throughout intrauterine life. "Oxygen environment" rose regularly to a maximum on the 100th day of gestation (90% saturation or more in the umbilical vein). This value gradually falls to about 70% saturation near term (near 145th day). There is an abrupt drop to 60% in the last week of intrauterine existence. The same characteristics were shown for the oxygen content of the blood in the umbilical arteries with one exception. As term approached, the oxygen content reached levels close to that of the umbilical vein. In other words, relatively much less of the oxygen brought to the fetus was retained by it in very late pregnancy than was retained by it earlier in pregnancy. This waxing and waning effect would tend to render many of the given figures for fetal blood oxygen content obtained through single measurements very unreliable.

Oxygenation levels of blood in the fetal brain rise and fall during gestation as well. Thus the degree of oxygenation of fetal blood falls gradually towards the critical level at which thoracic movements are induced. This would tend to support the theory that circulatory interruption and the resultant chemical stimulus produced, bring about respiratory movements. (This is in contrast to the fact that it is carbon dioxide tension that is the stronger stimulus in postnatal life).

Further evidence that chemical rather than physical stimuli are responsible for respiratory onset was furnished by Cohnstein and Juntz (1884). They partially removed a sheep fetus from its uterus. Subjecting the skin and the mucous membrane to physical stimuli, produced no results. Upon tying the umbilical cord, however, the fetus began to breathe. Thus circulatory interruption rather

than sensory stimuli was thought to be the most important factor in respiratory onset.

Occlusion of the cord inevitably results in elevated carbon dioxide and lowered oxygen levels in fetal blood. These two chemical stimuli, however, do not seem to be effective in inducing respiration in the asphyxiated non-breathing infant. Eastman (1932) offered the explanation that increased stimulation of the respiratory centre has a depressant effect. Three levels of human fetal respiratory existence can thus be visualized. The first is the normal situation, where fetal blood oxygen is a little lower and the carbon dioxide level a bit higher than in maternal blood. Under these conditions, no fetal attempt to breathe is made. In the second case, decreased oxygen content and (possibly only at birth) increased carbon dioxide content initiate respiration whether in utero or at birth. The greater anoxia of the third condition results in respiratory centre inactivity.

For the above theory to be of any value, evidence for the existence of chemoreceptors sensitive to chemical changes in the fetal blood stream must be obtained. Studies on the effects of high and low concentrations of oxygen on the respiration of premature and full-term infants (Cross and Oppe, 1952) may provide such information. Results obtained on infant studies were compared with those obtained in adult studies. It was found that there was very little difference in the minute volume changes (during the first minute of administration of 100% oxygen) of premature and full-term infants. There was, however, a much greater fall in minute volume in infants than in adults.

Premature and full-term responses to hypoxia (15% oxygen) were also very similar. Immediate hypoxic hyperventilation produced by increased respiratory rates that lasted four to five minutes were produced by administration of low concentrations of oxygen. Pulmonary ventilation declined to just below normal levels after the first four or five minutes of hyperventilation. While no statistical differences were indicated, Cross and Oppe (1952) suggested that premature infants were less able to sustain hypoxic hyperventilation than full-term infants. The adult results, however, showed sustained high minute volumes at comparable test periods.

The hypothesis proposed to explain the differences between the responses of infants and adults was based on the suggestion that infants have a much more active chemoreceptor reflex than adults. This highly sensitive chemoreceptor reflex, however, coexists with a respiratory centre that is unable to withstand oxygen lack. This system offers very poor defences against anoxia. The medullary centres are too rapidly depressed by anoxia to continue to respond to peripheral stimulation.

Basing their theory on the results of the above and additional fetal studies, Cross and Malcolm (1952) suggested that chemoreceptors are active before and after birth. Is there a structure, then, similar to the adult carotid body involved in the reflex control of respiration?

Boyd (1961) wrote of the existence, in the fetus, of a structure that is considered homologous and analogous to the adult carotid body. The cells of this inferior aortico-pulmonary glomus are derived from two embryological sources – neural and vascular. Its nerve supply is composed of conjoined bundles of vagal and sympathetic fibres. Its blood supply is derived from the pulmonary trunk. Argyrophil cells are present in the glomus from very early stages of fetal life. Although this structure has not yet been shown to possess an afferent nerve supply and the basic mechanism that renders this structure sensitive to changes in the blood circulating through them has not yet been discovered, its striking similarity to the carotid body suggests that it may have a function in the fetus similar to that of the carotid body in the adult.

In addition to the chemoreceptors of the inferior aortico-pulmonary glomus, "the carotid chemoreceptors in the human being, as well as in other species, are fully differentiated during embryonic life" (Reynolds and Mackie, 1961). Studies of the sensitivity of these chemoreceptors were made with the injection of small doses of sodium cyanide. Although hemodynamic effects (slowing of the heart, slight fall in blood pressure followed by a transient rise) were observed (Reynolds, 1953) with the administration of effective doses of cyanide, no respiratory responses were elicited. If, however, cyanide was injected during asphyxia or sensory stimulation, there was an accentuation of the expiratory effort. Intermittent artificial pulmonary ventilation also caused the fetus to be sensitive to small doses of cyanide. The response was abolished through vagotomy although stimulation of the cut end and artificial respiration re-established it. The above results indicate that cyanide causes no respiratory responses when the respiratory centre is inactive in the fetus. Thus a functioning or stimulated respiratory centre is required for chemoreceptor activity. This is of importance in the establishment of breathing at birth. Before birth, no respiratory responses are elicited by cyanide stimulation of chemoreceptors. Upon occlusion of the umbilical cord at birth, the accumulation of carbon dioxide in the blood excites the medullary respiratory centre. Partial pulmonary distention occurs with expansion of the lungs. The rate of blood flow through the lungs is increased. Stimulation of chemoreceptors can now augment the respiratory effort. The variations in the breathing patterns of the newborn can thus be attributed to the fact that, since the lungs are only partially distended and the efficiency of ventilation is low, the variable levels of carbon dioxide modify the sensitivity to chemoreceptor stimuli to varying degrees. In light of this, one can also speculate if the specific minimal tension of carbon dioxide that Snyder claimed (Snyder and Rosenfeld, 1937) was required for maintenance of fetal respiration was necessary to keep the medullary centre active.

THE FIRST BREATH

The first breath is characterized by a long expiratory phase and a short inspiratory component. Pressures up to 70 cm H_2O are involved. Pressure and volume changes are generally correlated especially during inspiration. There are no dramatic changes between the first and subsequent breaths. Pressure changes during the first breath range from 40 to 100 cm H_2O. An expiratory volume change (10-25 ml) and a positive pressure precedes the onset of the first breath in some babies. Pressure changes in subsequent breaths are similar but of decreasing magnitudes.

If the intra-esophageal pressure changes and respiratory volume changes were to be recorded for the first breath of a number of newborn, a wide range in volume (12-67 ml.) of the first visible inspiration would be observed. Most of the volumes recorded would be much larger than the tidal volumes of resting newborn infants with established respiration (15-20 ml.) but still less than the size of a maximal cry (130-160 ml.). The maximal cry can be considered as the vital capacity of a newborn infant. At one to two days after birth the functional residual capacity is 80-120 ml. Therefore, a reasonable inflation of the lungs is involved when the inspiratory volume of the first breath is considered.

When considering the cause of the first breath volume change, it is seen that an increase in volume of the surrounding thoracic cage as indicated by the high negative intra-thoracic pressure is responsible for the first breath. Diaphragmatic contraction is most likely responsible for this pressure drop because there is no compression of the thorax in roentgenologic studies after delivery and before the first breath. Diaphragmatic motion can also be shown by cineroentgenographic studies. In addition, the motions of the pharynx associated with the initial aeration of the lungs of the newborn infant was investigated using a high speed roentgenographic technique to analyse the motions of the pharyngeal area and the rapid aeration of the lungs at birth (Bosma et al, 1959).

A pharyngeal distention-compression sequence similar to the glossopharyngeal respiration ("frog breathing") of respiratory-deficient poliomyelitis patients was observed. It was suggested that this motion may actively inflate the lungs prior to the first thoracic inspiration. The lung and the pharynx were thusly inflated in three of the subjects studied. This preliminary glossopharyngeal "breath" prior to thoracic inspiration could create an instant of maximal initial pressure to overcome the cohesive force that would tend to limit the primary expansion of the lung. It would be, in effect, a "puff" method of initiating lung inflation.

The 10 to 70 cm H_2O negative pressures lasting 0.5 to 1 second generated in the first inspiration are necessary to overcome three resistive forces:

(1) Elastic tension of the lung tissue.

(2) Friction in the respiratory tract due to the flow of air and liquid.

(3) Surface tension in the respiratory tract due to the air-fluid interface.

The frictional forces are higher than they would be in later life because of the narrower airways and the higher density (than air) of amniotic fluid. The effects of the surface tension of the air-fluid interface necessitates an "opening pressure" during the first breath (20-40 cm H_2O). After this, inflation accelerates.

An irregular and prolonged impaired expiratory phase always follows the first inspiration without pause. This expiration has a high positive intrathoracic pressure (20-30 cm H_2O) associated with it. An upper respiratory tract obstruction has been suggested as the cause of this impaired expiration (Bosma et al, 1959). This impairment is associated with the rhythmical pharyngo - laryngeal closure seen roentgenologically during the first breath. This prevention of escape of air from the lung and the associated high positive pressure helps facilitate air distribution within the lungs.

Subsequent breaths have similar patterns to the first except that there is decreased inspiratory pulmonary flow resistance. Compliance is three to five times greater than that of the first breath in infants one to two days old. The pulmonary flow resistance is 2-4 times less in these infants as well. Therefore increased respiratory work is required only in the first three or four breaths. The total inspiratory work required, however, is of the same magnitude as that of a later neonatal cry.

There seemed to be an apparent failure to record a residual volume in Karlberg's (Karlberg et al, 1962) experiments. One would expect a continuously increasing end-expiratory volume to reflect the establishment of a residual volume. But it was only occasionally that a net volume difference was recorded and this was during the first visible breath. The explanation for this phenomenon may lie in the respiratory changes that may occur between the moment of delivery and the initiation of the first breath.

Considerable drainage of amniotic fluid from the respiratory tract due to compression of the thorax during delivery can cause the resultant elastic recoil of the thorax to create an inspiratory volume change. Gains from 0 to 40 ml. of air may result, while the functional residual capacity in the two-day-old infant ranges from 80 to 120 ml.

Pharyngeal movements (Bosma et al, 1959) prior to the first breath may also contribute to the aeration of the lungs. This is referred to as a "frog breathing" mechanism. Amniotic fluid is eliminated by swallowing. "Capillary erection" (Jaykka, 1954) has also been proposed as a possible explanation.

There is no further evidence of significant increases in residual volume after the first breath. This may be due to

the fact that subsequent increases take place in such small increments as to go unnoticed. Also, the gradual absorption of amniotic fluid through the alveoli would result in an imperceptible increase in aeration as well. In fact, the high positive intra-thoracic pressure of the first expiration may facilitate this absorption.

It has been assumed that lung air spaces are not empty but filled with amniotic fluid at the first inflation of the lung. The observation of intrauterine respiratory movements and the discovery of amniotic fluid in some infants suggest that a flow of fluid may occur (Farber and Sweet, 1931).

In fetal goats, the lungs are partially filled at birth and the pleural pressure is atmospheric. This is further evidence for the presence of fluid in the lung since lack of fluid would allow the outward recoil of the thorax to produce a lower pleural pressure (Avery and Cook, 1961).

Far from assuming that the fluid contained in lungs is derived from amniotic fluid, Jost and Policard (1948) suggested that the lungs themselves could possibly have contributed to the amniotic fluid. Upon tying off the trachea of a rabbit fetus, they observed an increase in lung volume. Distention of the alveoli with fluid in an anomalous fetal lung that is not connected to the trachea can also be noted (Potter and Bohlender, 1941). Contributions to the amniotic fluid could also be made by nasopharyngeal and buccal cavity secretions (Reynolds, 1953). A comparison of the protein content and osmotic pressure of tracheal effluent and amniotic fluid showed them to be similar. This was done by cannulation of the trachea of fetal goats and guinea pigs and by collection of fluid that would flow from the airways.

A more detailed study of the nature and origin of fetal lung fluid was made by Adams (Adams et al, 1963). It was found that the tracheal fluid of lambs had a lower pH (6.43) than that of amniotic fluid (7.07). A lower concentration of carbon dioxide was also evident in the tracheal fluid (4.4 mEq./litre as against 18.4 mEq./litre for amniotic fluid). The surface-active material, surfactant, that is normally found in lung air spaces was detected in tracheal effluent while it could not be detected by usual methods in amniotic fluid. Both the lung and the kidney excreted I^{131} and $Na^{22}Cl$ that was injected into fetal blood. This is very strong evidence that fetal tracheal fluid is an ultrafiltrate of blood. The differences in pH and carbon dioxide content are accounted for by the mixing of the ultrafiltrate with amniotic fluid from other sources. Now that the presence of fluid in the lungs has been established, it would be in order to speculate on its possible function.

Fluid within the fetal lung facilitates the entrance of air into the airless lung on the initial breath (Avery et al, 1959). LaPlace's relationship states that the pressure within a tube is directly proportional to the radius. Thus the radii of curvature of the alveolar ducts are enlarged by the fetal lung fluid and in this way, lung expansion is facilitated. Lung fluid also makes it less likely for inspissated material to obstruct the airways. Where this fluid goes after the initiation of respiration is a matter of conjecture.

However, three possible routes of exit can be postulated. It could leave through the airways. It could enter the blood circulation by way of the lymphatics. It could enter blood circulation from the alveoli to the capillaries. The latter route is perhaps the most likely. Since the lung fluid has a lower protein concentration than fetal blood, osmotic pressure could facilitate the absorption of the fluid from the alveoli into the capillaries.

SUMMARY

1. Intrauterine respiration does exist and the maximum respiratory rate is characteristic of fetal age. Respiratory movements are, therefore, not initiated at birth as previously thought.
2. A specific carbon dioxide concentration is required to maintain an active fetal respiratory centre.
3. Increased oxygen acts as a respiratory stimulus. Chemical rather than physical stimuli initiate breathing after birth.
4. An active chemoreceptor reflex exists in fetuses. It is active only when the respiratory centre is active.
5. Amniotic fluid exists in the fetal lung and serves a useful purpose at the initiation of extrauterine respiration by facilitating the entrance of air into the airless lung.

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Respiratory - Grand Round Quiz

by Dr. E. Grad
Associate Resident, Hospital for Sick Children

1) *Which of the following is* not true *in describing Idiopathic Respiratory Distress Syndrome:*
   a) can occur in full-term infants
   b) pathologically the lungs are hyperinflated with hyaline membranes lining the alveolar sacs
   c) is more common in the second born of twins
   d) is predominantly a disease of premature infants
   e) pneumothoraces occur in at lease 15% of the cases, whether or not they are on positive pressure ventilation

2) *Routine preschool chest X-ray on a six-year-old female revealed an elongated mass in the posterior mediastinum, extending from T_6-T_9. The most likely diagnosis is:*
   a) Thymoma
   b) Carcinoma of lung
   c) Sarcoid
   d) Ganglioneuroma
   e) Teratoma

3) *Answer True or False:*
   a) The treatment of choice for croup is Ampicillin.
   b) All cases of Epiglottitis should be put on steroids.
   c) High pitched inspiratory stridorous sounds with mucousy overtones heard over the suprasternal area may indicate a tracheal foreign body.
   d) A non-resolving croup with fever is a not uncommon feature of measles prodrome.
   e) Croup in a one-month-old infant is not unusual.

4) *A previously well, active 1½-year-old child develops the sudden onset of wheezing. There are no signs of associated URI and no family history of allergic manifestations. Physical examination reveals a well-developed and well-nourished child in no acute distress. The respiratory rate is 30/second. No cyanosis or clubbing. There are expiratory wheezes audible throughout the chest, more marked on the right side. Chest X-ray shows some air-trapping concomittant with the physical findings.*
   You would:
   a) Give adrenalin subcutaneously
   b) Put patient on antihistamine
   c) Give patient antibiotic and bronchodilator
   d) Ask for bronchoscopy
   e) Administer adrenalin subcutaneously, then give patient a prescription for bronchodilators.

5) *Answer True or False:*
   a) Pneumococcal pneumonia is the most common form of pneumonia encountered in childhood.
   b) Mycoplasma pneumonia is characterized by relatively innocuous clinical condition in comparison with X-ray findings.
   c) Staphylococcal pneumonia is characterized by a rapid clinical and radiological progression.
   d) Pulmonary Candidiasis occurs very frequently in infants because of the high incidence of oral thrush.
   e) The basic metabolic defect in Pulmonary Alveolar Microlithiasis (which is characterized by widely disseminated intra-alveolar calculi) is a defect in calcium and phosphorous metabolism.

6) *A six-year-old male child was admitted for treatment of staphylococcal pneumonia. Past history reveals four previous episodes of pneumonia. At age one year he was diagnosed as having Coeliac disease. On examination he was undernourished, poorly developed with 2^+ clubbing, widespread rales and rhonchi and R/R 50/second.*
   The most likely diagnosis here is:
   a) Agammaglobulinemia
   b) Food and Inhalant allergies
   c) Cystic Fibrosis
   d) Bronchiectasis
   e) Congenital Emphysema

7) *Answer True or False:*
   a) The most common site of primary lung abscess is the left upper lobe.
   b) Primary lung abscess generally occurs in an older age group than secondary lung abscess.
   c) The most common infecting organism is Staphylococcus.
   d) Treatment of primary lung abscess consists of Thoracotomy and drainage.
   e) Many patients with secondary lung abscesses die without specific treatment for the condition, and it is discovered on post-mortem.

FOR ANSWERS SEE PAGE 28

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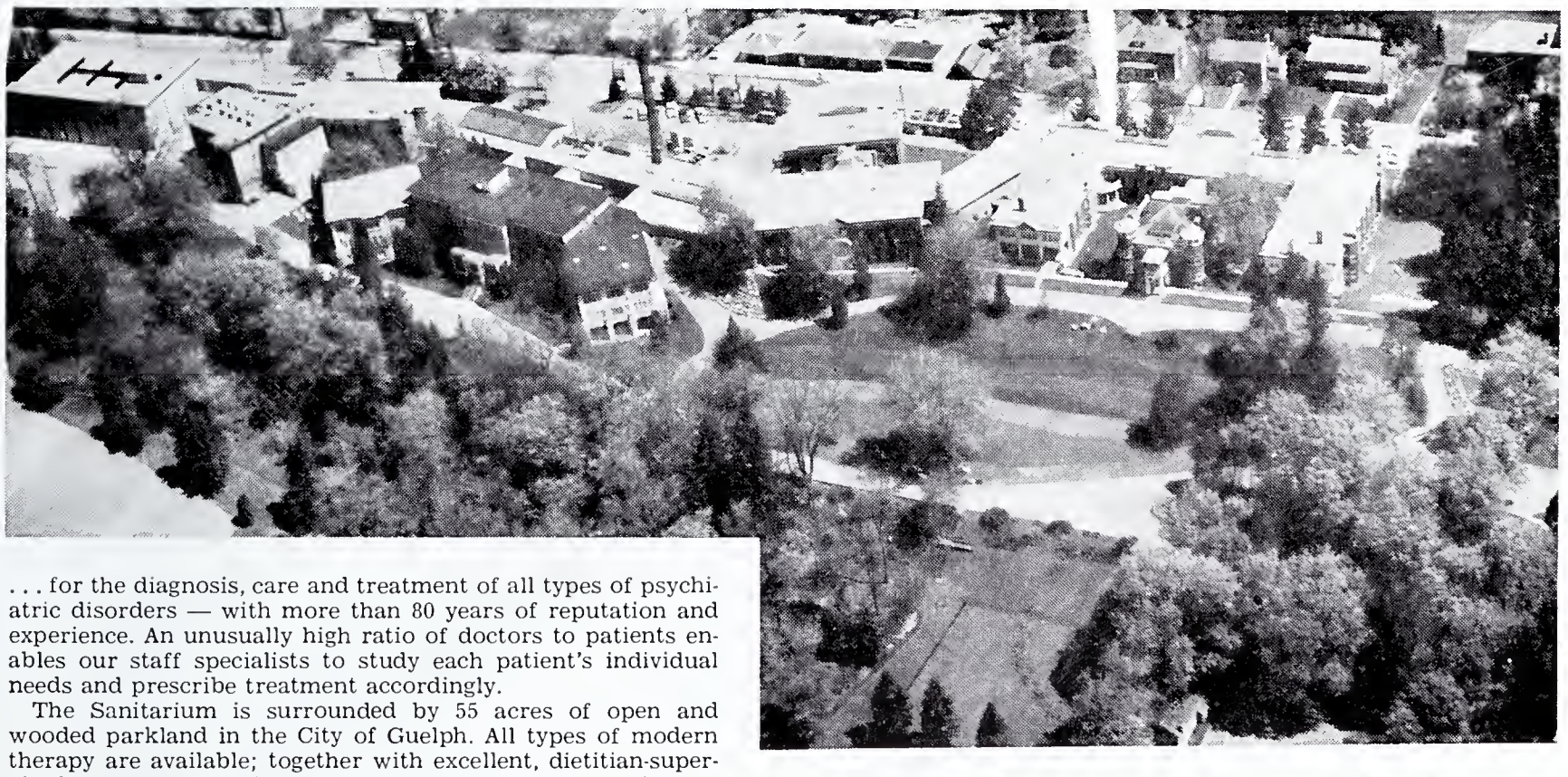

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Grand Round Quiz - Answers

1) (b) — Quite the opposite! The lungs are indeed underinflated and atelectatic. On X-ray one is immediately struck by the small volume of the lungs.
(a) — Slightly misleading. Although rare, RDS has been described in full-term infants (0.2% incidence).

2) (d) — Age, location and description of mass are more typical of ganglioneuroma.

3) (a) — False — Overwhelming number are caused by viruses and treatment is mostly directed at sedation, moisture and oxygen tent.
(b) — False — Too empirical a statement, no real proof it is valid.
(c) — True
(d) — True
(e) — False — If it occurs in a one month old, one should consider a congenital abnormality, such as subglottic stenosis.

4) (d) — Age, sudden onset and physical findings more marked on right side, would make one think of possible foreign body aspiration. Mother should first be questioned for history of foreign body aspiration.

5) (a) — False — It is the most common BACTERIAL form of pneumonia; but overall viral and intermediate agents account for the majority of cases.
(b) — True
(c) — True
(d) — False
(e) — False

6) (c)

7) (a) — False — Most common in apical segments of lower lobes (right greater than left).
(b) — True
(c) — True
(d) — False — Medical treatment with antibiotics and physiotherapy is becoming treatment of choice.
(e) — True

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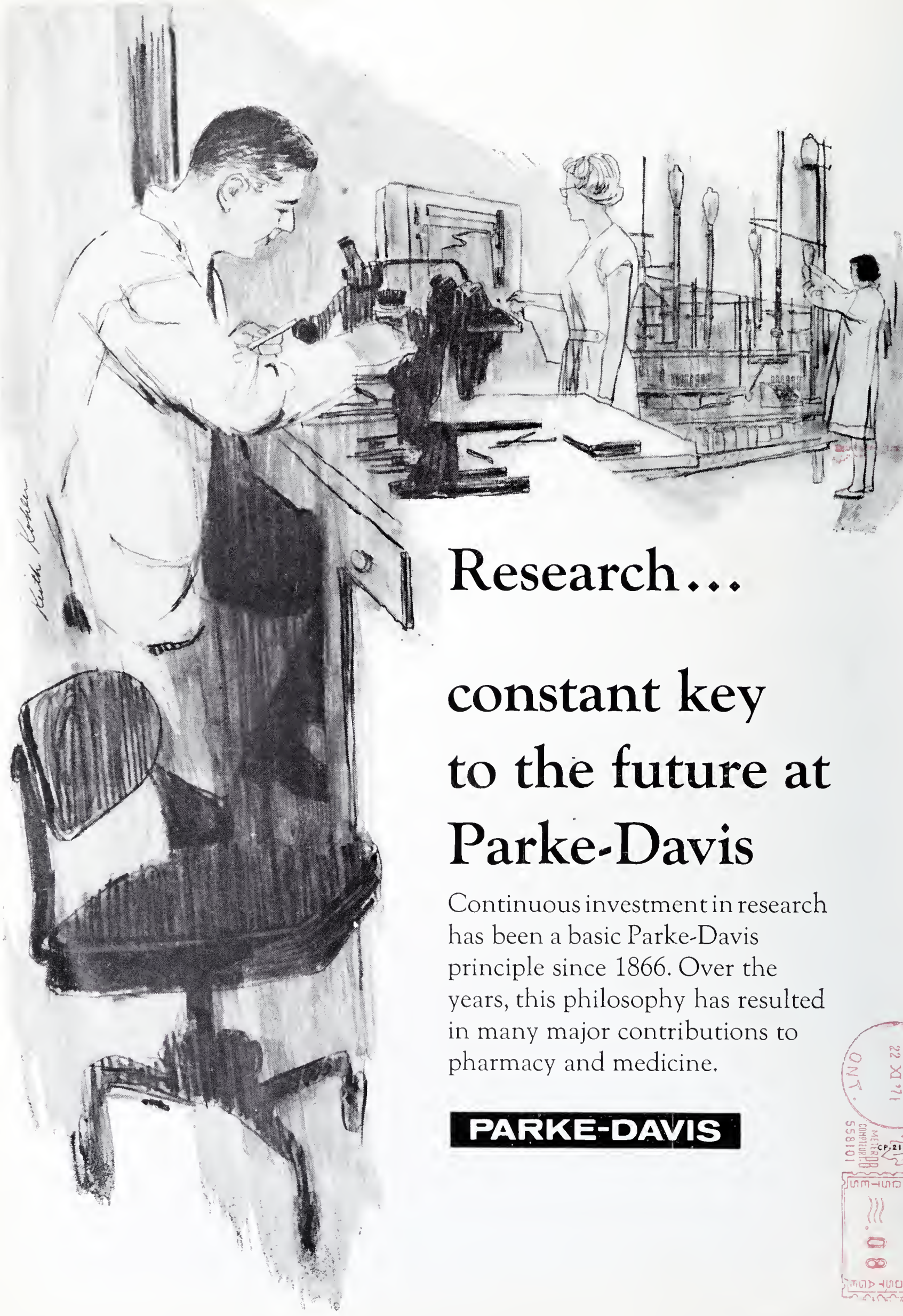

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